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Brain Architecture (2 ed.): Understanding the Basic Plan

Larry W. Swanson

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Thinking about the Brain : Body and Mind

Chapter: Thinking about the Brain
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"From what has been said, I shall draw the only conclusion that legitimately results; namely, that the mechanism of thought is unknown to us—a conclusion with which every one will probably agree. None the less the fundamental question I have suggested exists: for what concerns us is to know whether our present ignorance on this subject is a relative ignorance that will vanish with the progress of science, or an absolute ignorance in the sense of its relating to a vital problem that must forever remain beyond the ken of physiology. For myself, I reject the latter opinion, because I deny that scientific truth can thus be divided into fractions. It is difficult to understand how physiologists can explain the phenomena occurring in all the organs of the body, except a part of those occurring in the brain? Such distinctions cannot exist among vital phenomena. Unquestionably they present very different degrees of complexity, but they are all alike in being either soluble or insoluble by our examination; and the brain, marvelous as those metaphysical manifestations that take place in it appear to us, cannot form an exception among the other bodily organs."

Claude Bernard (1873)

"To extend our understanding of neural function to the most complex human physiological and psychological activities, it is essential that we first generate a clear and accurate view of the structure of the relevant centers, and of the human brain itself, so that the basic plan—the overview—can be grasped in the blink of an eye."

Santiago Ramón y Cajal (1909)

What is the brain, what does it do, and how does it do it? These intriguing questions were first raised—and examined within a scientific framework—by the ancient Greeks. Over the course of the next 2500 years, general answers from some of the greatest minds in Western culture have differed profoundly and generated deep controversy. Portia's song in Shakespeare's *Merchant of Venice* makes the point beautifully, "Tell me where is fancie bread/Or in the heart or in the head?"

Today we think of the brain as the organ controlling the nervous system, one of the 10 or so interacting functional systems the body is divided into by biologists—along with the skeletal system, circulatory system, digestive system, and so on. The nervous system is preeminent because of its two main functions. First, it directs the body's interactions with the external world by controlling behavior on the one hand, and by processing environmental sensory information through the eyes, ears, nose, tongue, and skin on the other. Thinking or cognition is a basic function of the brain in this interaction of the nervous system with the environment. And second, the nervous system controls the internal state of the body and processes visceral sensory information from the heart, stomach, genitals, and so on. Feeling or affect is a basic function of the brain in this control of the viscera by the nervous system. In short, the brain is a biological organ within the nervous system as a whole, the mind is a product of brain activity, and thinking and feeling are components of the mind.

How does the brain generate behavior—which in the end is simply the product of skeletomotor movements we can see other people and animals perform—and how does the brain generate thinking and feeling, which are internal conscious states we know from personal experience and infer in others? There are many scientifically useful ways to think about how the brain works. The abstract approach of philosophy and mathematical modeling lies at one end of the spectrum; psychology occupies the middle ground; and the physical sciences of biology, chemistry, and physics are at the other end of the spectrum. Considering all of these approaches in a synergistic, integrated way led to the emergence around 1970 of the powerful new interdisciplinary field of Neuroscience.

No matter how diverse, all aspects of neuroscience share one thing in common at the very core—the physical brain itself—and *Brain Architecture* focuses on the general organizing principles of its structural organization. What are the brain's parts, what does each one do and how does it work, and how are all the parts interconnected to form a system? And of course in a broader sense, what are the parts of the nervous system as a whole, how do they work, and how are they interconnected to control the rest of the body? In other words, what is the basic plan or blueprint of the brain, and more generally, the nervous system as a whole? This book is an attempt to distill the general principles of neuroscience that have stood the test of time, to present a new model of how the brain's functional systems are organized in a global sense, and to point out how much remains to be learned about what is far and away the most complex yet intrinsically interesting object that we know of here on earth.

If one theme dominates all others throughout the history of research on the brain—starting long ago with Hippocrates, Aristotle, and Galen—it would undoubtedly be *localization of function*, in more and more detail. This quest in turn requires accurate physical description of the brain at a finer and finer scale, and equally important, an accurate physical model of the brain and nervous system as a whole. There is no surprise here. One foundational lesson that emerges from the history of biology as a whole—and indeed from the history of modern systems analysis—is that accurate physical descriptions are necessary prerequisites for accurate functional understanding. In other words, logically valid conclusions about function cannot be drawn from inferences or experiments based on inaccurate physical models.

The greatest triumph of twentieth-century biology, the sequencing of the human genome, with its 3 billion base pairs, beautifully illustrates the fact that an accurate physical model is a prerequisite for functional understanding. This monumental achievement was based on a brilliant, elegant, and general structural model of DNA that was in turn based on extremely accurate physical data about the molecular components and their relationships (Fig. **1.1**). Once the logic of its structural organization was known, experimental proof followed, along with mechanisms of replication, the triplet code for making proteins from amino acids, and the creation of genetic engineering. Jim Watson and Francis Crick's double-helix model is taken for granted today, but a revealing twist to the story is that just 2 months earlier Linus Pauling, who was much more prominent and won the Nobel Prize a year later for his work on the nature of the chemical bond, had published with Robert Corey a different structural model for DNA—a triple helix! These were both elegant molecular models, but the one that turned out to be correct was based on more accurate and extensive structural data that to many biologists at the time might have seemed like trivial minutiae.





Figure 1.1
The young Jim Watson and Francis Crick admiring the large physical model they created for the molecular structure of DNA, which contains the genetic instructions used by all plants and animals. They worked on the problem in their spare time at Cambridge University's Cavendish Laboratory. Watson was a postdoctoral fellow and Crick was a graduate student. Their paper, “Molecular Structure of Nucleic Acids: A Structure for Deoxyribose Nucleic Acid,” was published on April 25, 1953, in *Nature*. Crick appended the paper to his 1954 PhD thesis on the X-ray diffraction analysis of polypeptides and proteins.

Two themes run through *Brain Architecture*. One is that a good model needs to be described and understood in terms of a set of clearly defined terms or concepts—a defined vocabulary, which is summarized in the Glossary—and a set of clearly defined relationships between the terms. This is becoming increasingly important as mathematical and computer science models of the nervous system start to be created. The second theme is that there are three common ways to simplify the understanding of complex biological systems. One is an historical approach because the larger, simpler, most obvious questions and approaches tend to occur to people earlier in time. Another is an evolutionary approach because simpler organisms tend to arise earlier in geological time. And the last is a developmental approach because the embryo starts out very simple—just one cell, the fertilized egg—and progressively differentiates over time. In other words, all three approaches proceed from simple to complex, approaching the same problem—the organization of the adult nervous system—from different angles.

Chapter 2 provides an historical introduction to the fundamental perspectives biology has provided to understand the mechanisms of life, including those of the nervous system. Chapters 3 and 4 trace the probable evolution of the nervous system and introduce the fundamental cell types that are the components of its biological circuitry. Chapter 5 outlines the embryological development of the vertebrate nervous system in terms of its basic topographic divisions. This provides the equivalent of geographic terms to describe location within the system. Then, Chapters 6–10 deal with the systemic or functional organization of the nervous system in terms of a basic four subsystems network model. The underlying premise here is that all connections in the vertebrate nervous system are part of either the motor, behavioral state, cognitive, or sensory subsystems. These four subsystems are arranged in a basic network (distributed) rather than hierarchical (top-down) wiring diagram, with each subsystem having its own characteristic organization: the motor subsystem that directly controls behavior is hierarchical, the divisions of the sensory subsystem are arranged in parallel, the cognitive subsystem is a network, and the behavioral state subsystem is like a sprinkler system. Chapter 11 deals with the fact that the nervous system, as part of the body as a whole, is alive and its structure–function organization is subject to constant modification by a wide range of factors throughout the life cycle. The book ends with a chapter considering a profound question for twenty-first-century biology: What is the relationship between gene networks and neural networks—between the genome and connectome?

Readings for Chapter 1

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How the Brain Works : History, Structure, and function

Chapter: How the Brain Works
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> *"From what has been said, the services of the brain are evident. They are of one sort according to Aristotle and of another according to Galen and his followers: look them up. It suffers ills of all kinds. Its injury is fatal, not always but most of the time."*
>
> Berengario da Carpi (1523)
>
> *"You can see these convolutions of the animal's brain [cortex] when you are at breakfast or dinner, but as to their functions both physicians and philosophers are greatly exercised. They dispute whether men have understanding through them or not."*
>
> Andreas Vesalius (1543)
>
> *"There are two ways only of coming to know a machine: one is that the master who made it should show us its artifice; the other is to dismantle it and examine its most minute parts separately and as a combined unit. Those are the valid methods of learning the contrivance of a machine… But, since the brain is a machine [Descartes, 1664], we need not hope to discover its artifice by methods other than those that are used to find such for other machines. There remains to be done, therefore, only what would be done for all other machines. I mean the dismantling of all its components, piece by piece, and consideration of what they can do separately and as a whole."*
>
> Nicolaus Steno (1669)

Most of us don't think much about our brain—let alone about how it works—until something goes wrong with it. Then we wonder why this or that awful symptom happened, and whether we can do anything about it. Stroke, depression, retardation, epilepsy, dementia, addiction, schizophrenia, autism… the list of heart-wrenching afflictions is long indeed, and it doesn't even include a host of other less severe yet frustratingly real problems like anxiety, learning and memory disorders, attention deficits, and so on. For answers, we often turn to medicine, to neurologists and psychiatrists who usually prescribe drugs or surgery that may relieve symptoms in a more or less effective way, at least for a while. But ask 10 of the world's leading neuroscientists how the brain works—how it thinks, feels, perceives, and acts as a unified whole—and you will get 10 very different answers, unless they are very narrowly framed around the biophysics and chemistry of nerve impulse conduction and synaptic transmission. Synapses are the functional contacts between nerve cells that may change their strength based on experience. You have about 100,000,000,000,000 of them in your brain, and they are so tiny their parts can only be seen with an electron microscope!

So there is no mystery about the uncertain state of affairs when it comes to explaining general principles of brain anatomy and function. Gram for gram, the brain is far and away the most complex object we know of in the universe, and we simply haven't figured out its basic plan yet—despite its supreme importance and a great deal of effort. There is nothing equivalent to the periodic table of the elements, relativity, or the theory of evolution to organize and explain a large (but still woefully incomplete and often contradictory) mass of information about brain structure and function. No Mendeleyev, Einstein, or Darwin has succeeded in grasping and articulating the general principles of its architecture, nor has anyone presented a coherent theory or model of its functional organization.

As a matter of fact, there is not even a list of basic parts that neuroscientists agree on, let alone a simple and clear account of what each part does, so how can there be a wiring diagram for the way they are interconnected to generate our thoughts, feelings, and actions? In view of this ignorance, it is little wonder that no real cures for any of the brain afflictions mentioned earlier have been stumbled on. New guiding principles based on understanding rather than fortuitous accident—and on a great deal more knowledge derived from research—are obviously needed before such cures will be discovered. This is the challenge of today's neuroscience.

We can only assume that these new principles will emerge in one way or another out of, or maybe in reaction to, what we already know about the brain, which is actually quite a lot. Many of the best thinkers throughout the long history of biology have contributed to the way we now view the physical underpinnings of behavior, thought, and feeling. By tracing the development of their basic ideas we can do two things. First, we can take stock of where we stand today, and second we can point out domains where we are still profoundly ignorant or could even be profoundly wrong.

If biology has taught us anything, it is that we can only understand the structure and function of the brain by considering them within the larger context of the structure and function of the body as a whole. On the one hand, there is no doubt that the brain controls the body. But on the other hand, the structure of the body as it develops in the embryo, and as it evolves over geological time, profoundly sculpts the structure of the codeveloping and coevolving brain. Thus, the basic organization of the nervous system as a whole reflects the basic organization of the body. The intellectual threads of this lesson can be traced easily and directly back almost 2500 years to Aristotle—son of the Macedonian king's physician, student of Plato, and father of comparative, developmental, and theoretical biology—the first curator of the animal world, as phrased so nicely by

Francis J. Cole.

Three Biological Perspectives

Aristotle's *Historia Animalium* (*History of Animals*) was the first and arguably still the finest textbook of animal biology ever written in terms of sheer originality, breadth, logical force, and lasting influence. He seems to have written it, along with two other brilliant books (*Parts of Animals* and *Generation of Animals*), while he was in his forties. This would have been before his final return to Athens, before most of his philosophical work was articulated at the Lyceum during the last decade of his life.

First and foremost, Aristotle's conclusions were based on an encyclopedic treatment of *personal observations* on a broad range of around 500 different types of animals. Nothing even remotely approaching this scope had ever been attempted before, and it gave him an unprecedented foundation in nature itself, rather than in speculation and folklore. And these comparative observations were not limited just to structure and function. In a strikingly modern way Aristotle paid equal attention to patterns of behavior, to ecological interactions, and to geographical distributions as well.

While this *comparative approach to the natural history of animals* in and of itself was a major contribution, it was only a starting point for Aristotle, who thought deeply about what the observations implied in terms of basic generalizations or principles. What emerged came eventually to be known as *theoretical biology* or *morphology*, an approach that today is gaining momentum, this time propelled by molecular genetics. As a matter of fact, it is the essence of Aristotle's theoretical work that has survived into modern times, stripped by Darwin of its preoccupation with “final causes” or preordained reasons. Experience has since amply demonstrated that this teleological approach of philosophers is a very easy and very unproductive way of thinking for scientists to fall into.

In his most brilliant theoretical synthesis, Aristotle suggested that just a small number of *basic body plans* can account for all the vast diversity of animal forms observed in Nature. Furthermore, he suggested that these body plans can be arranged in a hierarchy that is based on decreasing levels of complexity (with humans at the top, of course). Naturally, Aristotle's pioneering classification scheme has turned out to be incomplete and inaccurate. However, its basic form is obvious in the taxonomy graphs of any modern biology textbook. Here basic body plans are represented by the different phyla of the animal kingdom (vertebrates and assorted invertebrates: mollusks, arthropods, various worms, sponges, and so on), and the hierarchy is represented by an *evolutionary tree* rather than Aristotle's linear *scale of life*.

Aristotle's grand biological synthesis actually had a remarkable foundation on even more basic insights that are worth mentioning because they are still regarded as valid today. To begin with, in proposing the first scientific classification scheme for animals, he formulated the principle that judgments about affinities or similarities between animals have to be based on comparisons of all characters, not simply one obvious feature or another (like having wings). In doing so he had a fairly clear view of what we now call species and genera (Latin translations of terms that he actually used). Aristotle's basic concept that each major group of animals shares a common structural (body) plan or architecture extended to all the principal organ systems, and even included obvious positive and negative correlations between organ systems. This was the bedrock concept of Aristotle's first great successor two millennia later, George Cuvier (1769–1832). As part of this concept (“Cuvier's law of correlation of parts”), Aristotle emphasized that all animals belonging to a particular class have the same basic parts, which differ only by degree; in other words, they simply may be larger or smaller, softer or harder, and so on.

There is a flip side to the unity of plan principle—the tremendous biological diversity found in Nature. In dealing with this problem, Aristotle realized the importance of analyzing how comparisons of parts within as well as between major groups are actually made and interpreted. He recognized and began to articulate a fundamental difference between what we now call *homologous parts*, such as bones and teeth that have a common origin within a group, and *analogous parts*, such as bat wings and fly wings that have only a superficial resemblance between major groups. The real significance of homologous and analogous parts had to await the embryological and evolutionary work of the nineteenth century. In any event, Aristotle's preoccupation was in organs or functioning parts, rather than mere spatial relationships between parts. In one of his most brilliant excursions into morphology (“theoretical biology”) he compared cephalopod (e.g., squids, cuttlefish, and octopuses) organization, where the anus lies near the mouth (Fig. **2.1**), to a doubled-up or folded vertebrate body plan. Today, this view has received at least some support from work in molecular genetics.

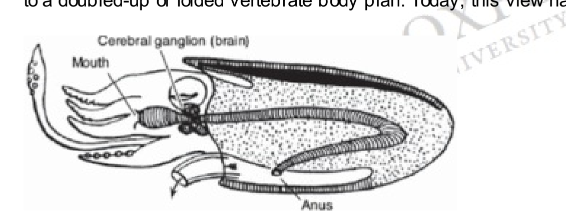


Figure 2.1
Basic body plan of the squid (a cephalopod). Note how the digestive system appears to fold back upon itself, so that the anus approaches the mouth. Also note the cerebral ganglion or brain, which lies dorsal to the esophageal region of the digestive system. Adapted from R. Hertwig, *Lehrbuch der Zoologie*, 10th edition (Fischer: Jena, 1912).

At another level of analysis, Aristotle made an equally fundamental set of distinctions related to a *hierarchy of body building blocks*. In today's vocabulary, he distinguished between *molecules, tissues, and organs*, and he even provided the first *classification scheme for tissues*. In his own vocabulary, Aristotle referred to elements (earth, air, fire, and water), homogeneous parts (roughly what we call tissues), and heterogeneous parts (organs). The importance of this analysis of body construction and organization can hardly be overstated. It was not until the middle of the nineteenth century—well over 2000 years later—that a fourth level of biological organization was added: cells.

And finally, credit goes to Aristotle for founding *developmental biology* through his brilliant naked eye descriptions all kinds of warm- and cold-blooded embryos, those of the chick and dogfish being the most thorough and famous. But of course he was not content with simply recording these observations. He went on to formulate the basic principle that *in embryology the general appears before the specific*—what came to be known as *Baer's law* in the first half of the nineteenth century. As Aristotle put it, an embryo is an animal before it is a specific animal, general characters appear before special characters, and tissues (homogeneous parts) appear before organs (heterogeneous parts). Based on vast observations and comparisons he even proposed an elaborate embryological classification of animals, another approach pioneered in modern times by Karl von Baer (1792–1876) and other nineteenth-century embryologists. And to top it all off, he advanced the strikingly modern idea that the unfertilized egg is like a complex machine whose wheels move and function as designed after a master switch is thrown.

For all his genius, Aristotle's theorizing and lack of anatomical data (in his time blood vessels and ligaments were not distinguished from nerves) led to the conclusion that the heart rather than the brain is the seat of the intellect—even though some of his greatest predecessors came to the opposite—modern—conclusion. They included Pythagoras, Pythagoras's pupil Alcmaeon (who in the sixth century BC is thought to have carried out dissections, during the course of which he discovered the optic nerves), Hippocrates (c. 460 BC–c. 370 BC), and his contemporary, Plato. The modern application of the *experimental method* to the life sciences by William Harvey and others in seventeenth-century Europe eventually led to the irrefutable resolution of this conflict in the nineteenth century by Pierre Flourens (1794–1867) and Friedrich Goltz (1834–1902). The intellect is in the brain, and as a matter of fact, it is a product of neural activity in a specific division, the cerebral hemispheres.

As we will see now, the comparative, embryological, and theoretical approaches to biology pioneered by Aristotle have led to major insights into the basic structure–function organization of the nervous system. They have provided invaluable ways to make sense out of—to see fundamental patterns in—the vast diversity of animal life. The intellectual debt we owe him was phrased beautifully in a letter written by Charles Darwin just 2 months before he died: “Linnaeus and Cuvier have been my two gods, though in very different ways, but they were mere schoolboys to old Aristotle.”

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The Simplest Nervous Systems : Neurons, Nerve Nets, and Behavior

Chapter: The Simplest Nervous Systems
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> *"All the organs of an animal form a single system, the parts of which hang together, and act and react upon one another; and no modifications can appear in one part without bringing about corresponding modifications in all the rest."*
>
> George Cuvier (1789)

It is easy to imagine that over the course of evolution here on earth, which spans on the order of 5 billion years, the simplest organisms appeared first, and when viewed over a very long time frame they were followed by more and more complex organisms, culminating with the appearance of modern humans only 100,000 years ago or so (Fig. **3.1**). Continuing to think along these lines, it seems like a good bet that we should be able to learn a great deal about nervous system architecture by starting to examine it in the evolutionarily oldest, simplest organisms, and then going on to analyze its organization in progressively more recent and complex organisms, before considering it finally in the ultimate puzzle, the human brain. By then we should have a vocabulary and set of rules that apply to all mammals, to all vertebrates, and perhaps even to all animals with a nervous system.

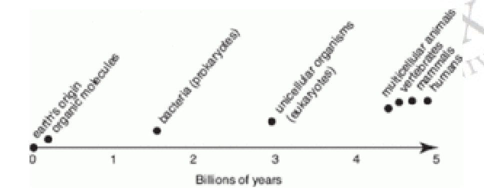


Figure 3.1
The evolution of life on earth has occurred over roughly 5 billion years.

Unfortunately, this line of reasoning has flaws, not the least of which is that soft tissues like those forming the nervous system leave no fossil record behind. We can detect no trace of what the nervous system actually looked like in fossils of the earliest multicellular animals (called Metazoa), which finally appeared on earth sometime around 600 million years ago, and it is hard to imagine how such evidence could ever be obtained. Facing up to this reality, but steadfastly remaining intrigued with the possibility of learning something basic about nervous system organization, comparative biologists have turned to modern descendants of the various early animal phyla in trying to reconstruct a plausible evolutionary scenario or tree—while freely admitting that these living groups of animals have undoubtedly evolved or changed to some extent (sometimes even becoming simpler) during the long period of time since they first appeared on earth.

The most succinct and appealing reconstruction along these lines was presented by the Harvard zoologist George H. Parker (1864–1955) in a delightful little book, *The Elementary Nervous System*, which was published in 1919, well after Darwinism had conquered all aspects of biology. The following discussion is based loosely on his general line of reasoning, fleshed out with discoveries made since then. Parker's approach was to examine each fundamental building block or unit of the nervous system (in other words, each neuron type) from the viewpoint of its basic structure and what it adds to the functional capabilities—in particular the behavior—of the animal as a whole.

Parker's conclusion, like Cajal's before him (see section on "Motor Neurons: A Second Distinct Neuron Type"), was that *neuron types are defined best by their connections* within neural networks, in other words, *by their inputs and, even more important, their outputs*.

Unicellular Organisms: Behaviors Essential for Survival

It is important to stop and realize before going any further that individual species of the single-celled organisms called Protozoa may be surprisingly differentiated and show rather complex behaviors—obviously in the complete absence of a nervous system (Fig. **3.2**). Fortunately, modern biology can now explain most of this behavior in terms of biochemical reactions and the molecular architecture of individual cells and their parts. To begin with, it is critical to appreciate that (as is true for all cells in all living organisms) a *plasma* or *cell membrane* forms the boundary between the inside of the protozoon and its external environment, and there is an *electrical potential* (that requires energy from a molecule called ATP to maintain) across the membrane. Under normal resting conditions, the inside of the cell is negatively charged relative to the outside. We

will return shortly to the importance of this membrane electrical polarization for information signaling in the nerve cells of multicellular animals.

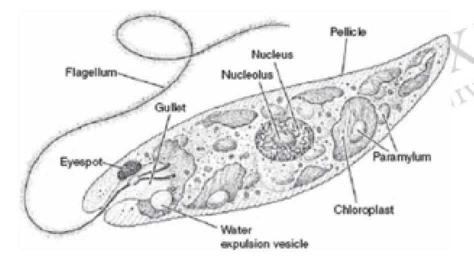


Figure 3.2
The basic structure–function organization of a single-celled Protozoa, Euglena. Note specializations like a photosensitive eyespot, a gullet for taking in and processing nutrients, a water expulsion vesicle for regulating intracellular fluids, a chloroplast for energy production, and a “motor” (the flagellum) for navigating the environment. Reproduced with permission from R.C. Brusca and G.J. Brusca, *Invertebrates* (Sinauer: Sunderland, 1990, p. 132).

Ethology is the scientific analysis of behavior, and a vast literature of brilliant research has shown that all Protozoa and Metazoa alike display *spontaneous or intrinsic activity*, and that this activity includes at least *three fundamental classes of behavior that are necessary for survival of the individual and the species as a whole: ingestive, defensive*, and *reproductive*. Generally speaking, ingestive behavior is concerned with regulating nutrient supplies and internal water balance. In multicellular animals we usually think of these activities in terms of *eating* and *drinking*, but in single-celled animals they involve regulating the *movement of nutrients and waste materials*, and of *water*, across the plasma membrane and through the interior of the cell.

At the risk of stating the obvious, water is the single most important component of any cell. All biochemical reactions take place in the cell's aqueous medium, which forms at least 90%–95% of the cell mass, and water balance regulation is critical to the cell because there are osmotic forces (which unregulated cause shrinking or swelling) across its membrane, essentially because the concentration of various molecules is different inside and outside the cell.

A more or less continuous supply of nutrients to fuel *metabolism* is also obviously required—metabolism generates the *energy supplies* (for example, ATP) for maintaining membrane potentials, synthesizing *organic molecules*, and so on. In Protozoa, nutrients enter from the environment, and/or are derived from intracellular organelles called chloroplasts that are driven by the energy from light (Fig. **3.2**).

Mechanisms for ingestive behavior in Protozoa can be surprisingly sophisticated. For example, *Paramecia* have a channel in the plasma membrane called a gullet or oral groove that participates in taking in food, they have systems of vacuoles (membrane-bound bags) that shuttle food around and digest it inside the cell, and they even have a relatively fixed site for the expulsion of waste product vacuoles called an anal pore. And don’t forget, many Protozoa can use cilia or flagella to swim toward sources of food or away from environmental threats (Fig. **3.2**).

The route of this locomotor activity, which we call *foraging* or *exploratory behavior* in “real” animals, is directed by nutrient-associated chemicals in the environment that are detected by plasma membrane *receptors*. These receptors are proteins that help activate the cilia or flagella in ways that cause the protozoon to swim toward the highest concentration of nutrient—in essence, to approach the food. Generally speaking, this type of protozoan behavior is referred to as a *taxis*, and the specific type just described is referred to as a *positive chemotaxis* because the cell swims toward the highest concentration of a particular chemical (behavior that depends, of course, on expressing the right kind of receptors in the plasma membrane). This is a form of *approach behavior*.

In contrast, *defensive or avoidance behavior* in Protozoa often involves swimming away from rather than toward toxic chemicals in the environment, using mechanisms that involve *negative chemotaxis*. This class of behavior is obviously critical for survival of the individual protozoon, and it may also be triggered by other stimuli such as touch or temperature gradients. Some Protozoa, especially those with a flagellum, even have a light-sensitive eyespot or stigma (an aggregation of light-sensitive pigment) that helps regulate the direction of swimming behavior (Fig. **3.2**). These eyespots illustrate the principle that receptors specific for particular types of stimuli (light, touch or mechanical deformation, temperature, and chemicals, for example) can be highly localized on or in some particular region of a protozoon. And very important, these receptors may show *adaptation*—that is, the response may decrease (or perhaps increase) on repeated exposure to a particular stimulus. This leads to modified or *learned behavioral responses*—in other words, behavior that is altered by past experience—although in Protozoa this learning does not appear to be associative (see Chapter 12).

Finally, most Protozoa—and even some bacteria—display both sexual and asexual *reproductive behavior*s. The former have the great advantage of producing in the offspring genetic variation, which is the fodder for Darwinian evolution based on a natural selection of the most adaptive individuals in a diverse population—individuals with the greatest probability of reproducing to perpetuate the species.

The survival of an individual requires appetitive or consummatory behaviors as well as defensive or avoidance behaviors, whereas survival of the species requires reproductive behaviors. In humans we refer to ingestive, defensive, and reproductive classes of motivated behavior, and the search for systems in the brain that control them is an active area of research.

Animals without Neurons: Independent Effectors

Sponges are the simplest multicellular animals, and yet they took around a billion years to evolve from Protozoa, arriving on the aquatic scene a half a billion years ago or so. Perhaps not surprisingly, their body plan is more like a colony of specialized protozoa than the rest of the animal kingdom, which has much more highly structured embryos with a basic architecture consisting of three stacked layers of cells. As we will see in the next section, these layers go on to produce distinct tissues in the adult, including nervous tissue. Sponges are so primitive and unusual that it was not until the second half of the eighteenth century that they were even recognized as animals instead of plants!

The simplest multicellular animals like sponges have two important adaptive advantages over unicellular animals: first, their larger size provides greater resistance to physical stresses in the environment; and second, they are not in fact a simple colony of protozoa. Instead, they have evolved different cell types—a *division of labor* that increases efficiency for specific tasks like nutrition and defense.

Sponge behavior can be described rather easily and succinctly: they are sessile suspension-feeders (Fig. **3.3**). In other words, they make relatively boring pets. They are immobile, attached at their base to the bottom of some marine or fresh-water environment, where they exchange nutrients (along with gasses and wastes) from water circulating through their body. Conceptually, *their body is just an immobile, asymmetric or radially symmetric bag* with many tiny holes or pores scattered throughout a relatively thin body wall. Environmental water flows through these pores into the animal's inner cavity (spongocoel), and then out into the environment through a large hole at the top (osculum). This circulation of water through the pores to the spongocoel and then back out through the osculum is promoted by the beating of flagellated (Fig. **3.2**) cells, which create a current, lining the inside of the spongocoel.







Figure 3.3
The simple body plan of sponges. As indicated by arrows, water flows through body wall pores into a central cavity and then back out into the external environment through a hole in the top of the central cavity. From G.H. Parker, *The Elementary Nervous System* (Lippincott: Philadelphia, 1919, p. 26).

The regulation of water flow through the sponge's body amounts to the relatively simple regulation of their feeding behavior. This is accomplished by a *specialized cell type* that is fundamental to our story of how metazoans control their behavior. These cells are called *myocytes*, and they have a critically important property, *contractility*, that allows them to shorten and thus do work. For example, these elongated cells are arranged concentrically around the pores in the sponge body wall, where their contraction allows them to act as sphincters, controlling the rate of nutrient- and oxygen-containing water flowing through the animal.

Sponge myocytes are probably distant ancestors of the *smooth muscle cells* that coat and regulate flow through our own blood vessels, like at precapillary sphincters. For myocytes in sponges to contract and slow the flow of water, they must be stimulated directly. For example, they may contract when directly stretched, or they may contract or relax when certain chemicals interact with certain corresponding classes of receptors in their plasma membrane.

Based on functional considerations, Parker referred to myocytes as *independent effectors*. That is, myocytes (or independent effectors in general) are cells that produce a *motor response* when directly stimulated—without, to anticipate our story, the intervention of neurons.

Sponges are uniquely simple multicellular animals without a nervous system. However, their feeding behavior is regulated by independent effectors—smooth muscle cells whose contraction is directly regulated by mechanical, chemical, or thermal stimuli. The response of these myocytes to such stimuli is relatively slow and sustained compared to the response of neurons, as we are about to see. In addition, myocytes are much less sensitive to stimuli than neurons. In other words, it takes a much larger stimulus to produce a response in myocytes as compared to neurons, and typically these responses are much slower and last much longer in myocytes. And finally, the whole plasma membrane surface of myocytes may be able to detect stimuli—input stimuli may act anywhere on the surface of the cell.

The First Nervous System: Hydra's Body and Behavior

Jellyfish, corals, sea anemones, and hydra are among the simplest animals with a nervous system, and because of this their nervous system is the simplest to understand, as far as architectural principles are concerned. Their phylum (Cnidaria) has a radially symmetrical body plan, and like all other multicellular animals but sponges they have a three-layered embryo. The outer layer ("skin") faces and interacts directly with the external environment and is called the *ectoderm*. The inner layer lines a cavity inside the animal ("gut lining") and is called the *endoderm*. And a multifunctional middle layer in between, which is a primitive mesoglea in Cnidaria, is called the *mesoderm*.

There are two main reasons the common laboratory hydra provides a favorite example of how the basic neuron types of the nervous system may have evolved originally. First, hydra has an elegantly simple body architecture. Fundamentally, there is a mouth at one end of its body tube and a foot at the other. And second, compared to sponges hydra has very intriguing patterns of feeding and locomotor behaviors (Fig. **3.4**). These animals bring food to their mouth with a set of tentacles, which they also use in an ingenious way to locomote through the environment by tumbling. These complex, stereotyped behaviors require waves of patterned muscular activity to pass up and down the body and tentacles, in coordinated ways that are not used at all by sponges, which as we have just discussed have independent effectors but no nervous system.

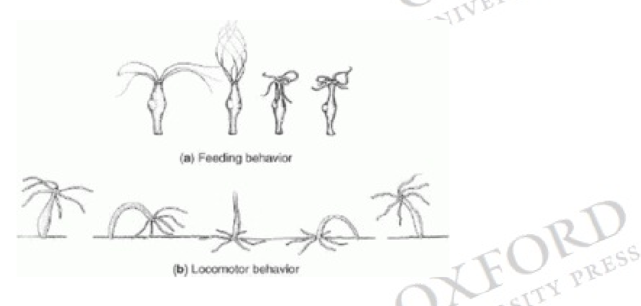


Figure 3.4
Two fundamental classes of behavior in hydra, among the simplest animals with a nervous system. Example (*a*), feeding behavior, is reproduced with permission from H.N. Lenhoff, Activation of feeding reflex in *Hydra littoralis*, *J. Gen. Physiol*., 1961, vol. 45, p. 333. Example (*b*), locomotor behavior, is reproduced with permission from J.L. Gould and W.T. Keaton, *Biological Science*, sixth edition (Norton: New York, 1996, p. 1068).

Sensory Neurons: Functional Polarity of Dendrites and Axon

Hydra use their tentacles like paddles to wave food into their mouth, and this paddling may be initiated by nutrient detectors near the ends of the tentacles that trigger their *rhythmical movements*. These detectors are *sensory neurons*, and they are the first of three fundamental types of neuron, based on a structure–function classification scheme.

The prototypical sensory neuron is derived from the outer or ectodermal layer of the animal. It is a *bipolar cell*, with a *detector*, *sensory*, or *input* end directed toward or into the environment, and an *effector*, *motor*, or *output* end going to a group of responsive cells like myocytes (Fig. **3.5**). The independent effectors we discussed for sponges—which have low sensitivity, slow activation, and prolonged activity when stimulated directly—can also be regulated by neurons that are highly sensitive and fast acting. In other words,

effectors like myocytes can now be regulated in two ways, independently as before and by the nervous system as well. In addition to speed and sensitivity, sensory neurons have the advantage that they can be highly localized in various parts of the body, like at the ends of tentacles. This provides a restricted and specialized source of inputs to effector cells or, as we will see, to other types of neuron.

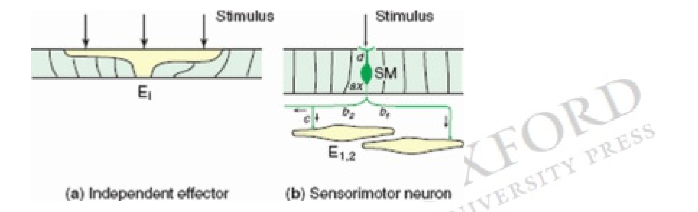


Figure 3.5
Two basic cell types involved in producing behavior. (*a*) Independent effectors (E_i, yellow) in a layer of cells (light green) do not require activation by neurons, and receptors for stimuli from the environment may occur anywhere on the cell's surface (plasma membrane). (*b*) The sensory neuron shown here in the outer or ectodermal layer (light green) is actually a special case, a sensorimotor neuron (SM, dark green), because it both detects stimuli and directly regulates effector responses like contraction or secretion. This simple bipolar neuron has one extension (pole *d*, dendrite) that reaches into the environment and is specialized to detect a particular type of stimulus, and another extension (pole *ax*, axon) that conducts information about the stimulus away from the dendrite and cell body to a set of effector cells ($E_{1,2}$) that also may be regulated directly by nonneuronal stimuli. Somewhat confusingly, neuron extensions are also referred to as “processes.” The axon trunk emerging from the cell body bifurcates deep to the ectodermal layer containing the sensorimotor neuron, and each bifurcation branch (b_1, b_2, which may be asymmetrical) in turn generates axon terminals (filled green circles) on effector cells—either directly (from b_1) or from an axon collateral (*c*). Arrows show direction of information flow.

Sensory neurons beautifully illustrate two principles that are at the very heart of contemporary neural network analysis. The generality of these principles was convincingly demonstrated around the end of the nineteenth century by the crown jewel of Spanish science, Santiago Ramón y Cajal (1852–1934), who used a histological method developed in 1873 by the Italian master, Camillo Golgi (1843–1926). The first is the *neuron law* or doctrine, which is nothing more than the cell theory proposed by botanist Matthias Schleiden (1804–1881) in 1838 and the zoologist Theodor Schwann (1810–1882) in 1839—applied to the nervous system. It simply points out that the nervous system is formed by a network of self-contained units or cells (nerve cells or neurons) that generally interact by way of contiguity or contact, rather than as a continuous syncytium formed by the extensions of neurons, as Golgi and most of his predecessors thought. The second principle is called *functional polarity* (also known as dynamic polarization). It states that the output side of the neuron is typically a single extension called an *axon*, whereas the input side of the neuron typically consists of a *cell body* (with its nucleus and chromosomes—the DNA blueprint for the cell), along with one or more extensions (also known as processes) called *dendrites*. These principles allow for predictions about the direction of information flow through neural networks based on the shape of their constituent neurons—axons and dendrites are generally easy to tell apart because they have distinct structures.

Information flow along individual neurons is by way of electrical signals conducted via the plasma membrane of the dendrites, cell body, and axon. The amplitude of these signals may be proportional to the strength of a stimulus (that is, graded), as they often are in dendrites; or the amplitude may be of uniform size (that is, all or none), as they are in axons and sometimes in dendrites. However, it is critical to know that this information is transferred to another cell (such as a muscle cell or another neuron) at specialized sites called *synapses*. At a conventional chemical synapse, *neurotransmitters* are released into the extracellular fluid from specializations called presynaptic *axon terminals*. Mixtures of receptors in the membrane of postsynaptic cells detect the released batch of neurotransmitter molecules, and go on to *(a)* trigger an electrical signal in those cells, and/or *(b)* trigger metabolic or molecular changes in them.

This combined-sequential electrical then chemical transmission of information is common to all nervous systems from hydra to humans. In fact, basic cellular neurophysiology is similar from hydra to humans. What changes dramatically through the course of evolution is the arrangement of the three fundamental neuron types discussed in this chapter into more and more highly organized systems or networks.

The axon of sensory neurons displays one especially important structural feature that probably applies to all axons: *divergence*. That is, every axon generates multiple synapses, usually from distinct branches or collaterals (which were originally emphasized if not discovered by Golgi in 1873). Because of this, an individual sensory neuron can *innervate* (provide synapses to, that is, provide an input to) more than one effector cell—for example, it might contract a group of myocytes rather than a single myocyte. Different branches might even innervate more than one cell type, for example, myocytes and secretory (gland) cells. Independent effectors act alone, whereas output from a sensory neuron can provide input to and activate a set of “independent” effectors almost simultaneously. On the other hand, branches from more than one sensory neuron may end on one effector. This is a feature referred to as *convergence* in neural systems. One sensory neuron may innervate more than one effector cell (divergence), and each effector cell may be innervated by more than one sensory neuron (convergence).

Thus, the relatively insensitive, slow, long-lasting, and individualized responses of independent effectors may be augmented by sensory neurons, which can display extreme sensitivity, can respond quickly and rapidly, and can influence sets of effector cells. These are major adaptive advantages provided by neurons: sensitivity, speed, amplification, and coordination, not to mention the potential for highly localized distribution patterns within the animal's body.

Motor Neurons: A Second Distinct Neuron Type

In considering sensory neurons up to this point, we have been describing a “one-layered” nervous system: a layer of what are usually called sensory neurons in the ectoderm or outer layer facing the environment that *project* or send an *output* of axons to a “layer” of effector cells like myocytes. In fact, to be completely accurate and consistent, the sensory neuron illustrated in Figure **3.5** ought to be called a *sensorimotor neuron* because it detects environmental stimuli *and* it projects directly to effector cells. In reality, all Cnidaria actually have at least a “two-layered” nervous system. In the simple example illustrated in Figure **3.6**, effector cells like myocytes are innervated by a second fundamental type of neuron, *motor neurons* (often shortened to motoneurons) instead of directly by true sensory neurons, which instead innervate the motor neurons.

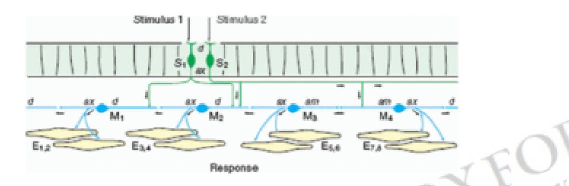


Figure 3.6
The principle of a “two-layered” nervous system, one with sensory (S) neurons and the other with motor (M) neurons. Note how quickly neural network complexity may increase with just these two basic neuron types, largely because of divergence and convergence. One sensory neuron (S_1) is specialized to detect one class of stimulus (Stimulus 1) with its dendrite (*d*), and its axon (*ax*) bifurcates to innervate two motor neurons ($M_{1,2}$), each of which in turn innervates two effector cells ($E_{1–4}$). Note that the axon of M_2 synapses with the dendrite of M_1, so that M_1 gets convergent inputs from S_1 and M_2. Thus, activation of S_1 influences four effector cells and the response in $E_{1,2}$ is amplified by convergent synapses or inputs to M_1. Another sensory neuron (S_2) is specialized to detect a different class of stimulus (Stimulus 2) and its axon trunk branches to

innervate a different (partly overlapping) set of motor neurons (M_2, M_4, M_x). Motor neurons M_3 and M_4 are somewhat unusual because in place of a dendrite they have an amacrine extension (*am*). These extensions are specialized to conduct electrical signals in either direction because they have bidirectional (reciprocal) synapses, with synaptic vesicles on both sides of the intracellular synaptic cleft. The functional consequences of this are clear by examining the activation of M_3, which can be done by way of S_2 input to M_4, but not by way of S_1 input to M_2. It is obvious that adding a second "layer" to the nervous system (compare with Fig. **3.5** *right*) greatly increases the complexity of responses that stimuli can induce in sets of effector cells. Arrows show direction of information flow.

What are the adaptive advantages of adding a second neuron type to the hydra nervous system? First, separating sensory and motor functions—a "division of labor"—adds the important possibility of regulating these two basic neuron types independently. In principle, the potential for more regulation provides the potential for more complex behavior. Second, this two-stage or two-layer nervous system has even more divergence and convergence than a (theoretical) one-stage system because the axon of both sensory and motor neurons typically has multiple branches to multiple postsynaptic target cells. The situation where one sensory neuron innervates and excites multiple motor neurons, each of which in turn innervates and excites multiple effector cells in a "pyramid of excitation," was referred to as *avalanche conduction* by Cajal. And third, motor neurons in hydra commonly interact with other motor neurons by way of tangential or "horizontal" extensions (Fig. **3.6**), whereas sensory neurons tend not to interact directly with one another.

Clearly, sensory and motor neurons have distinct structures and functions. Sensory neurons detect various classes of environmental stimuli—chemicals, temperature, light, touch—and project to motor neurons, whereas motor neurons by definition project to nonneural effector cells (and often to other neurons), and receive inputs from both sensory and other neurons.

This leads to a fundamental conclusion about *how to classify, or really how to identify, different neuron types*—like classifying various species of trees or varieties of dogs. After unparalleled experience and reasoning, Cajal came to the conclusion that the best criterion is the connections of the neuron, and especially the distribution of the axon—which in the end defines a great deal about the functional significance of a neuron. What does it innervate, and thus influence? What does it do functionally? A comparison of the basic connections of sensory and motor neurons in hydra illustrates this principle clearly, and it can be extended to the entire nervous system. Cerebellar cortex organization in vertebrates is another terrific example; half a dozen or so very clearly defined neuron types are arranged in a highly stereotyped way, with clear input–output relationships.

Nerve Nets: Amacrine Extensions and Activity Patterns

In hydra, motor neurons are scattered more or less uniformly throughout the body wall and tentacles, and they interact with one another by way of short, tangentially oriented extensions that tend to conduct graded electrical potentials, that is, electrical signals that get weaker the farther they spread along a neuron extension. As a result, when the nervous system of hydra is viewed as a whole it has the appearance of what has been called for a century or so a distributed or diffuse *nerve net* (Fig. **3.7**).

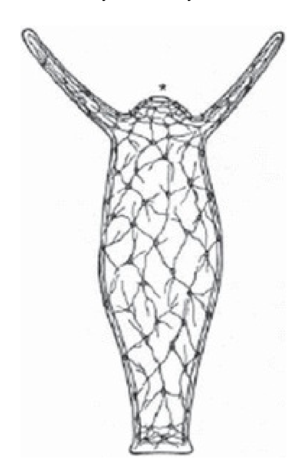






Figure 3.7
A schematic view of the nerve net in hydra. Note that the nerve net is slightly specialized in at least two places: near the hypostome ("mouth"; indicated by asterisk) and near the base ("foot"). From C.F.W. Claus, K. Grobben, and A. Kühn, *Lehrbüch der Zoology* (Springer: Berlin, 1932, p. 221).

Curiously, most hydra motor neuron extensions fall into one of two classes: an axon that conducts electrical signals to nonneural effector cells, and the tangential extensions that conduct electrical activity between the motor neurons themselves. Under normal conditions, many of the tangential extensions conduct in either direction and have a terminal with synaptic vesicles loaded with neurotransmitter at the end, which is related to a tangential extension of another motor neuron that also has a vesicle-laden terminal at the end (Fig. **3.6**, *am* between M_3 and M_4). In other words, many of these tangential extensions act functionally as both a dendrite and an axon, depending on whether a naturally activated electrical potential spreads toward or away from the cell body. This functional arrangement is possible because there are *bidirectional chemical synapses* at the points where two extensions from different motor neurons interact.

Neuron extensions that normally conduct in either direction, and establish what amount to bidirectional (reciprocal) synapses with like extensions, were recognized as a separate functional category, now called *amacrine extensions*, by Cajal. He did this to distinguish them from dendrites, which normally transmit information toward the axon, which in turn normally transmits information away from dendrites and the cell body. According to this scheme, neurons can have *three functionally distinct types of extension: axonal, dendritic, and amacrine.*

The simplest way to think about the functional significance of hydra nerve net architecture is to imagine that a stimulus applied to any one part of the animal will cause neural activity to spread diffusely through the net from the point of stimulation, and the strength of activity will decrease with distance from the point of stimulation because conduction tends to be decremental in amacrine extensions and dendrites. That is, in a nerve net stronger stimuli will spread farther, and produce greater responses, than weaker stimuli. It is easy to imagine that activity initiated by food on or near the tip of a tentacle could spread down the tentacle, producing the paddling motion responsible for bring food toward the mouth—and that "better" food (in the sense of a stronger stimulus) might lead to more vigorous paddling that extends to adjacent tentacles. Furthermore, the exact arrangement of amacrine extensions and dendrites can bias the direction of spread in a nerve net (Fig. **3.6**).

Even in hydra, it is an exaggeration to say that neurons of the nerve net are uniformly distributed throughout the body. In fact, there is some increased density of cell bodies—*a consolidation or differentiation of the nerve net*—in regions like the foot, mouth, and base of tentacles, where rudimentary *nerve rings* may be distinguished. These rings are specialized to control specific functions, like the diameter of the mouth or tentacle movement during feeding and locomotion, and they are more obvious in more complex Cnidaria like jellyfish.

While nerve nets with extensive amacrine extensions seem to have appeared at the earliest stages of nervous system evolution, they have survived throughout the animal kingdom. For example, they are found in restricted, critical parts of the human brain like the retina (amacrine cell layer) and olfactory bulb (granule cell layers), and in the lining of the human digestive system.

Interneurons: Sign Switchers and Pattern Generators

A third fundamental neuron type—in a sense, a third layer or stage—may be found in the vaguely differentiated nerve rings of hydra: *the interneuron* (Fig. **3.8**). By definition, interneurons are neither sensory nor motor neurons; on connectional grounds they lie in between. There is a seemingly infinite variety of interneurons. However, they can be divided for the sake of convenience into two broad classes: *intraregional (local) interneurons*, with an axon that ramifies entirely within the gray matter region that generates it; and *interregional (projection) interneurons*, with an axon that ramifies within the gray matter region where it is generated and/or projects to another gray matter region.

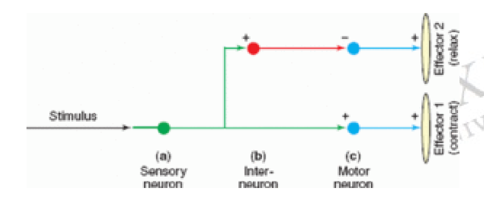


Figure 3.8
Interneurons lie between sensory and motor neurons. Together, these three basic neuron types can be arranged in a "three-layered" nervous system, with functional connections established between individual neurons by way of three types of cytoplasmic extensions (processes): axonal, dendritic, and amacrine (Fig. **3.7**). In the specific example here, the axon of a sensory neuron (green) branches to provide an excitatory (+) input to a motor neuron (blue) and an inhibitory (–) interneuron (red). Because both motor neurons provide an excitatory (+) input to an effector (in this example a muscle cell), a stimulus to the sensory neuron will lead to contraction of effector 1 and relaxation of effector 2, an interesting pattern of behavior.

Adding a third and final basic neuron type, with more and more varieties in more and more complex animals, provides animals with even more adaptive advantages, mainly in the realm of providing for increasingly sophisticated organization of neural networks, and thus behavior. A third level of control is added, and the potential for divergence and convergence is expanded even further, probably exponentially.

But interneurons provide two additional features that are critically important for nervous system function, although they have not been discussed as yet: *excitatory/inhibitory switching* and *pattern generation*. In discussing chemical transmission between neurons (at synapses), we have assumed up till now that stimulation of a sensory neuron will lead to stimulation of a motor neuron—an excitatory input from sensory to motor neuron. However, transmission through neural networks involves both *excitatory (+)* and *inhibitory (–) synapses*. If one branch of a sensory neuron axon synapses directly on a motor neuron and another branch synapses on an inhibitory interneuron that innervates a second motor neuron, the first motor neuron will be excited, whereas the second will be inhibited (Fig. **3.8**). Thus, in this simple example, an inhibitory interneuron acts as a switch from excitation to inhibition in the network. In its simplest form, this network produces *central excitation* and *lateral inhibition*.

A second basic function of interneurons is to act as pattern generators. As a matter of fact, the inhibitory interneuron just discussed may be thought of as a simple pattern generator. When the sensory neuron under consideration is excited, the first motor neuron is excited and produces a response, whereas the second motor neuron is inhibited and thus does not produce a response (Fig. **3.8**). This is a stereotyped pattern of behavior (admittedly very simple) elicited by stimulating a sensory neuron.

As a matter of fact, the dynamics of nerve nets, and of neural networks in general, are even more interesting. Many if not all sensory, motor, and interneurons appear to display *spontaneous neural activity*, so that they are almost always capable of producing a pattern of electrical impulses if left entirely alone. Because of this, excitatory synapses tend to increase basal neuronal firing patterns, whereas inhibitory neurons tend to decrease these firing patterns. One illuminating consequence of this spontaneous "background" electrical activity is that excitation of motor neurons tends to increase muscle contraction or tone, whereas inhibition of motor neurons tends to decrease muscle contraction (that is, it relaxes muscles). In short, synaptic inputs tend to modulate the firing rate of a neuron around some "spontaneous" or baseline rate, or setpoint.

The *spontaneous, intrinsic activity of nervous systems* is a profound concept because it invalidates the *behaviorist view of animals* that was fashionable in the first half of the twentieth century—the view that animals passively wait for external stimulation to trigger behavior in a purely reflex way. Quite to the contrary, the nervous system is spontaneously active, the nervous system is alive, and its activity is simply modulated—not controlled entirely—by external stimulation.

As mentioned earlier, the structural organization of interneuron extensions allows them to form pattern generators within neural networks. In addition, however, their spontaneous activity can be utilized in truly ingenious ways, for example, to *generate spontaneous rhythmical activity patterns* (as in the tentacles), or even as *"biological clocks"* in many animals.

Overview: Evolution of Architecture, Not Building Blocks

Neurons first appeared during evolution in the Cnidaria, and their basic structure and function have stayed remarkably constant throughout the rest of the animal kingdom, including in the human brain. Neurons in all animals can be divided into three fundamental types: sensory, motor, and interneurons. Generally speaking, information is transmitted along neurons and their three types of extensions (axon, dendrite, amacrine) via electrical impulses associated with the plasma membrane, whereas it is usually transmitted between neurons and other cells via chemical synapses that use a mixture of neurotransmitters (although some *electrical synapses* are known). What has evolved dramatically is the complexity of nervous system organization—not its individual units or neurons.

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Oxford Medicine







Brain Architecture (2 ed.): Understanding the Basic Plan

Larry W. Swanson

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Centralization and Symmetry : Ganglia and Nerves

Chapter: Centralization and Symmetry
Author(s): Larry W. Swanson
DOI: 10.1093/med/9780195378580.003.1027

> *"Without the relevant unifying concepts, comparative neurology becomes no more than a trivial description of apparently unrelated miscellaneous and bewildering configurational varieties, loosely held together by a string of hazy 'functional' notions."*
>
> Hartwig Kuhlenbeck (1967)

So far, we have considered Protozoa and sponges, unicellular organisms and multicellular animals without a nervous system, along with the simplest animals with a nervous system—the jellyfish, corals, sea anemones, and hydra that have a more or less diffuse nerve net. All of these organisms either lack symmetry or are radially symmetrical, and their bodies are so simple that they lack clearly differentiated tissues. These features change dramatically when we come to what is commonly regarded as the next major branch of the evolutionary tree, the flatworms (phylum Platyhelminthes).

Flatworms: Bilaterally Symmetrical Predators

These flat, unsegmented worms swim forward through the water very efficiently in search of food or a mate, or to escape predators (Fig. **4.1**). Not surprisingly, the front end of the animal, which technically is called the rostral (for the Latin *rostrum*, originally the beak of a ship's prow) end, contains specialized sense organs for detecting and identifying objects that the animal approaches as it locomotes through the environment. Now, for the first time, we encounter a bilaterally symmetrical body plan, with a longitudinal median plane that divides it into right and left halves, and extends from rostral to caudal (for *cauda* or tail) end. In addition, because the body is flat, there is a very clear top and bottom, technically referred to as dorsal (for *dorsum* or back, the "top" in this case) and ventral (for *venter* or belly, the "bottom" in this case) surfaces. Rostral/caudal and dorsal/ventral are the basic directional terms used to describe positional or topological relationships in all bilaterally symmetrical animals, including humans, although actual geometrical relationships often lead to confusion (see Appendix A). They are analogous to the north/south and east/west pointers on maps of the earth. In other words, there are perpendicular rostrocaudal and dorsoventral axes. A third axis perpendicular to the first two completes the scheme. It is called the mediolateral axis. Medial indicates a position toward the median plane, and lateral indicates a position toward the right or left edge of the animal.



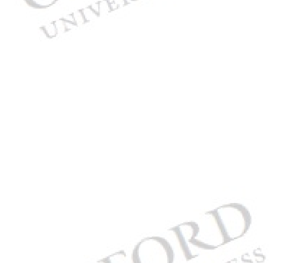




Figure 4.1
The basic architecture of the flatworm (planarian) nervous system as viewed from above. Th ere are two longitudinal nerve cords extending caudally from right and left lobes of the cerebral ganglion (brain) in the head region (at the top, rostrally), numerous transverse commissures between the cords, and transverse nerves lateral to the cords. The caudal end of the nervous system is arranged as a plexus. Note that three cardinal axes can be recognized in this animal: rostrocaudal ("head to tail"), mediolateral ("right-left"), and dorsoventral ("back to belly"); see Appendix A. Reproduced with permission from T.L. Lentz, *Primitive Nervous Systems* (Yale University Press: New Haven, 1968, opposite p. 73).

A glance at Figure **4.1** reveals a strikingly organized nervous system in flatworms, compared to the nerve net in Cnidaria. It is immediately obvious that there is a massive condensation of neural elements into a right and left *longitudinal* (rostrocaudal) *nerve cord* and a series of *transversely* (mediolateral) oriented *commissures* between the nerve cords and *nerves* lateral to the cords, and that there are also major condensations of nervous tissue in the rostral end ("head") of the animal. The latter are associated with specialized sensory and motor mechanisms in the part of the animal that scans the oncoming environment during swimming.

The trend toward condensation of neural tissue is referred to as *centralization*, and it involves the aggregation of axons or nerve fibers (an axon with or without a myelin sheath), and of neuron cell bodies (also referred to as somata, or sometimes perikarya—actually the cell body minus its nucleus). In the nineteenth century, the distinguished English philosopher Herbert Spencer and then Cajal argued convincingly that centralization leads to *(1)* a conservation or more efficient use of biological material in the construction of neural networks, *(2)* shorter distances traversed by neuron extensions to accomplish topologically similar network connections, and consequently *(3)* all things remaining equal, shorter conduction times for electrical impulses. These efficiencies of material, distance, and time would seem to be an almost inevitable consequence of evolution over immense periods of time, and they were foreshadowed by Dante's immortal aphorism, *omne superfluum Deo et Naturae displiceat* (everything superfluous is displeasing to God and Nature). Spencer had the distinction of anticipating Darwin in his famous argument that as a general rule the entire scope of organic evolution is accompanied by a change from the homogeneous to the heterogeneous, from the simple to the more complex.

More careful study of Figure **4.1** shows that the nervous system outlines the basic organization of the body. Each side of the rostral, head region contains a relatively large mass of neurons, a "lobe of the cerebral ganglion," that is pretty much bilaterally symmetrical and connected by an "isthmus of the cerebral ganglion" across the midline. This mass, the *cerebral ganglion* or *invertebrate brain*, and its differentiation in more complex animals, is associated with a concentration of special sensory and motor systems in the head. The elaboration of centralization in the rostral end of the body during evolution is referred to as *cephalization*.

An obvious, thick nerve cord extends down the right half and the left half of the body from the right and left lobe of the brain, and these two cords merge or anastomose near the tail of the animal in a complex, irregular, net-like arrangement called a *plexus*. Because of their sheer volume and localization, the brain in the head region, and the two longitudinal nerve cords with their commissures in the trunk region, form the *central nervous system* in flatworms. The isthmus of the brain, along with the nerve cord commissures (central transverse communicating branches), obviously allow information to pass from one side of the body to the other side. Nothing remotely as differentiated or condensed as this arrangement is found in the radially symmetrical, very sluggish Cnidaria with more or less condensed nerve nets.

Sensory information about the environment in front of the head is gathered by various receptors and processed in the brain, which in turn controls swimming (locomotor) behavior by sending commands down the nerve cords. This swimming behavior is triggered by waves of muscle contraction passing along the animal's body from rostral to caudal, and the precise timing and right-left balance of these waves determines the route taken by the animal, and the speed used along the route. The sequential activation of muscles along the body is actually coordinated by information that is distributed by a ladder-like arrangement of thinner, transversely arranged nerves, which also carry sensory information from the body to the thicker longitudinal cords. This is the *peripheral nervous system*, as opposed to the central nervous system. Thus, from a strictly gross anatomical or topographic perspective we may refer to a *central nervous system* and a *peripheral nervous system*.

It is immediately obvious that the flatworm's brain, cords, commissures, nerves, and plexuses form an anastomotic network or reticulum when viewed with the naked eye (Fig. **4.1**). However, just as in hydra, the actual connectivity of this nervous system is formed by tiny individual neurons that are linked together by chemical synapses or switches in very complex, stereotyped, genetically determined networks—it is not a continuous cellular reticulum. The actual course of axons from specific neurons or neuron groups within and through the latter-like arrangement of anastomotic cords, nerves, and brain is an exceptionally difficult problem to solve, with plenty still to be learned.

As neural elements condense and centralize during the course of evolution, they tend to form two broad classes of structure: collections of neuron cell bodies that are called *ganglia*, and bundles of axons (or more generally, nerve fibers) referred to as *nerves*. For the vertebrate central nervous system it is becoming unfashionable to refer to ganglia. Instead, it is preferable to reserve the term *ganglion* for a cluster of nerve cell bodies in the invertebrate nervous system and vertebrate peripheral nervous system.

It is within the ganglia and central nervous system that most synapses between neurons occur. In the ganglia of invertebrates, nerve cell bodies tend to lie around the outside or periphery, and most synapses, which are axodendritic, occur in the center, where the tissue is called *neuropil* (a complex mixture of axons, dendrites, synapses, and glial cell extensions when present). Central parts of the invertebrate nervous system also have considerable regions of neuropil, although its arrangement is much more irregular and complex than in typical ganglia.

In flatworms, and in all other invertebrates except the Cnidaria, most interneurons and motor neurons are *unipolar* (Fig. **4.2**). They have an ovoid cell body, a single massive extension—the axon—that courses for a longer (in, for example, motor neurons and *interregional interneurons*) or shorter (in, for example, *intraregional interneurons*) distance, and a multitude of thin dendrites that extend transversely from the proximal region (closest to its origin from the cell body) of the axon. This is in stark contrast to vertebrates, where instead the vast majority of interneurons and motor neurons are multipolar, with one or more dendrites extending from the cell body, and an axon that arises from the cell body or one of the dendrites.

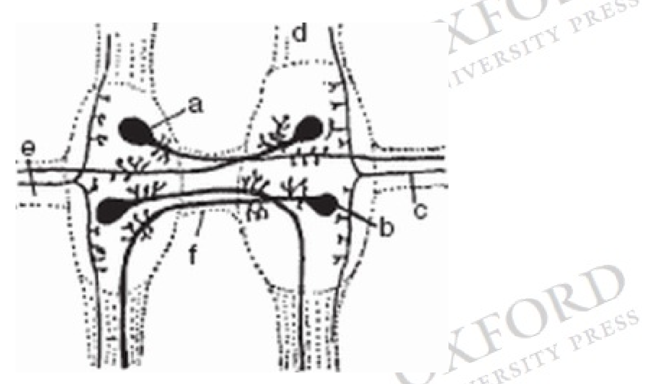


Figure 4.2
The typical appearance of unipolar neurons in invertebrate ganglia of two (right and left) nerve cords. Key: a, motor neuron with crossed (commissural) axon; b, commissural or sensory association neuron; c, bifurcating sensory fiber from the integument; d, central longitudinal communicating branch; e, nerve containing outgoing motor axons and incoming sensory axons; f, commissure or central transverse communicating branch. From S.R. Cajal, *Histologie du système nerveux de l'homme et des vertébrés*, vol. 1 (Maloine: Paris, 1909, p. 16).

The fact that most invertebrate synapses are formed in an incredibly fine-grained neuropil, whereas most vertebrate synapses are formed on the massive dendrites of neurons that are easy to identify led Cajal to conclude that neural circuitry is much easier to elucidate in vertebrates than in invertebrates. This was based on his valiant though personally disappointing attempt at the neuroanatomy of the ant after publishing his masterpiece on the histology of the entire vertebrate nervous system.

Segmented Worms: Internal Ventral Nerve Cord

Earthworms and leeches are typical examples of the some 15,000 species of segmented worms in the Annelid phylum, which has a more sophisticated body plan than the simpler flatworms—segments, which technically are called metameres, are serially repeating body units. In Annelids the nervous system has become even more centralized and the brain lies dorsal to the rostral end of the digestive system—accounting for the term *supraesophageal ganglion*, which is sometimes used for the brain in these animals. However, in the segmented worms, and in all other invertebrates except Cnideria, the major longitudinal nerve cords, the central nerve cords, come to lie next to each other ventral to the gut, or they fuse into a single ventral nerve cord in that location (Fig. **4.3**).

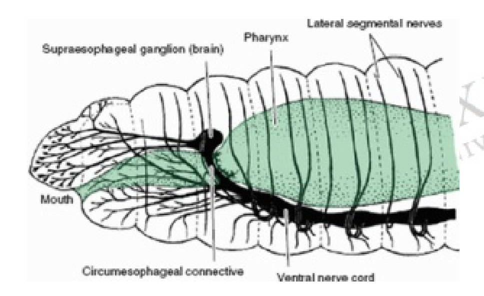




Figure 4.3
The basic arrangement of the nervous system in the rostral end of the earthworm (annelid). Relative to the digestive system (green) the brain is dorsal and the nerve cord containing the segmental subpharyngeal ganglia (slight swellings in each segment) is ventral. Note that the distribution of peripheral nerves is more complex in the rostral end ("head region") of the animal. Adapted from W.N. Hess, Nervous system of the earthworm, *Lumbricus terrestris L*, *J. Morphol*., 1925, vol. 40, p. 238.

The composition of the ventral nerve cord in segmented worms is interesting, and its embryological origin seems to differ fundamentally from the analogous spinal cord in vertebrates. As the name implies, one basic way segmented worms differ from flatworms is that much of their body length is formed by the serial repetition of a transverse unit called a *segment*. The basic idea is that this arrangement is a genetically efficient way to program the development of a more complex animal because essentially the same genetic program can be used over and over—in each segment or metamere.

Each body segment in an earthworm, for example, has a ventral ganglion and paired (right and left) nerves that circle dorsally and ventrally to innervate various parts of the segment. In the adult, these segmental ganglia more or less fuse and are also bound into a cord by the presence of innumerable longitudinally oriented axons. The organization of neuronal interconnections in this ventral nerve cord is even more complex than it is in the ganglia discussed for the flatworms—implying that more complex behaviors are mediated by this circuitry (compare Figs. **4.2** and **4.4**).

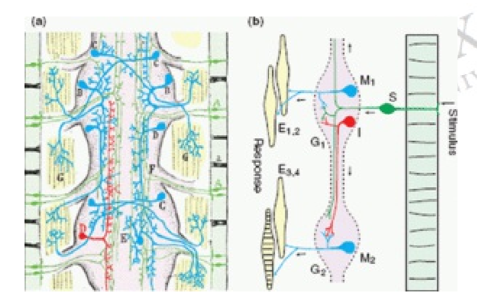


Figure 4.4
Some features of neural network organization in two sequential earthworm subpharyngeal ganglia (see Fig. **4.3**) as viewed from above. The network now consists of three basic structure–function classes of neuron: sensory neurons (green), interneurons (red), and motor neurons (blue). (*a*) This drawing is based on Golgi-impregnated tissue and shows both the right and left sides of the body, with ectoderm in light green, ventral nerve cord and its subpharyngeal ganglia in light red, and muscle in light yellow. Key: A, sensory neurons; B, ipsilateral motor neurons within a subpharyngeal ganglion; C, motor neurons with crossed axon; D, interneuron with ipsilateral longitudinal bifurcation branches; E, multipolar motor neuron; F, bifurcation of sensory neuron axon trunk; G, terminal arborizations of motor neurons on muscle. Adapted (colored) from S.R. Cajal, *Histologie du système nerveux de l'homme et des vertébrés*, vol. 1 (Maloine: Paris, 1909, p. 5). (*b*) This more schematic drawing shows only sensory input from a stimulus on the right side of the animal, and one of many possible motor responses on the left. Based on the selection of neurons illustrated here, the axon trunk of a sensory neuron (S) bifurcates in the upper ganglion (G_1) and a collateral of the caudally directed bifurcation branch innervates two other neurons: the dendrite on one motor neuron (M_1) in G_1 that innervates two effector cells ($E_{1,2}$) and the dendrite of an interneuron (I) whose axon innervates the dendrite of a motor neuron (M_2) in the lower ganglion (G_2) that innervates two more effector cells ($E_{3,.4}$). Arrows indicate presumed direction of information flow.

More Evolved Invertebrates

There are many invertebrate phyla that have a more highly differentiated body plan than the flatworms and segmented worms: insects, crustaceans, mollusks, and so on. At one end of the spectrum is the tiny fruit fly, which has been the favorite of neurogeneticists for a century, and at the other is the giant octopus, with a brain that at least superficially puts many vertebrates to shame in terms of sheer size and complexity (Fig. **4.5**). Nevertheless, they all have a dorsal brain, and a ventral nerve cord that lies between the gut and the ventral body wall. It is remarkable that the brain and ventral nerve cord of invertebrates are derived from the ectodermal layer of the embryo—the layer where the sensory and motor neurons of the hydra nerve net are also generated. During embryogenesis, these ectodermally derived neurons migrate into the interior of the animal (that is, into the mesodermal layer), in a process that is called *delamination*.

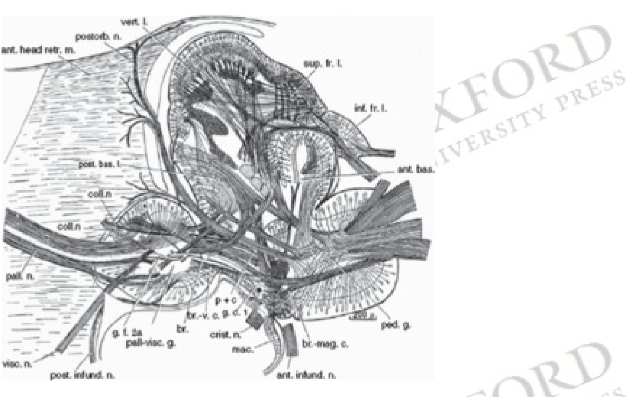




Figure 4.5
The brain of a young octopus viewed in a parasagittal section. The octopus brain contains on the order of 150 million neurons. Rostral is to the right. Reproduced with permission from J.Z. Young, Fused neurons and synaptic contacts in the giant nerve fibres of Cephalopods, *Phil. Trans. R. Soc. B*, 1939, vol. 229, p. 471.

Overview: Polarity, Regionalization, Bilateral Symmetry, Segments

Before delving into the basic plan of the vertebrate nervous system, let's pause for a moment to consider what we have learned about the biology of the “simpler” organisms. In the first place, recall that even unicellular organisms like Protozoa display three classes of remarkably sophisticated behaviors that are actually common to all animals because they are essential for survival: ingestive (eating and drinking), defensive (fight or flight), and reproductive (sexual and parental).

Second, the most primitive multicellular animals (sponges) also have no nervous system, and yet they display the same three classes of behavior. These animals evolved various cell types that are specialized for particular tasks; they have seized upon the advantages associated with the division of labor principle. The myocyte is one of these cell types, and it is able to contract when directly stimulated. The activity of these independent effectors allows the animal to regulate the availability of nutrients and oxygen much more effectively than in Protozoa.

Third, the radially symmetrical Cnidaria display a new cell type, the neuron, that is arranged in a more or less diffuse nerve net now controlling the activity of the (former) independent effectors in a much more effective way, and allowing yet more sophisticated feeding and even locomotor behaviors. The fundamental morphology, physiology, and chemistry of individual neurons, as well as their mode of functional contact with other cells, are remarkably similar in all animals.

And fourth, the evolution of bilateral symmetry in animals (first in worms) is associated with *(a)* localized condensations or centralization of the nervous system into ganglia, nerve cords, commissures, nerves, and plexuses; *(b)* polarity in the sense that there is a head at one end and a tail at the other end; *(c)* regionalization of the nervous system such that there is a highly differentiated brain in the head, and nerve cords in the trunk and tail; and *(d)* segmentation of the nervous system and the rest of the body. As with nerve nets in Cnideria, the ganglia, nerve cords, commissures, nerves, and plexuses of worms are found in all “higher” animals. In humans, the division of the nervous system in the wall of the digestive system is a plexiform nerve net, nerves and ganglia are the principle components of the peripheral nervous system, and the great sympathetic chains are bilateral nerve cords.

Readings for Chapter 4

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Oxford Medicine



Brain Architecture (2 ed.): Understanding the Basic Plan

Larry W. Swanson



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The Basic Vertebrate Plan : Transverse Divisions

Chapter: The Basic Vertebrate Plan
Author(s): Larry W. Swanson
DOI: 10.1093/med/9780195378580.003.1034

> *"A diagram is a changing structure. It must be improved, now here, now there. Certain parts often need to be torn down and rebuilt. It has been contended that we ought not to make use of diagrams in a subject so full of gaps as is our knowledge of the structure of the nervous system. Let us rather hold, with old Burdach, who wrote in 1819, 'The gathering together of material for the building is not all that is necessary. Every time that a new supply is obtained, we should renew our attempts to fit it into the building. By thus giving it a form the spirit of investigation is not hampered in its advance; on the contrary, it is when we first obtain a view of the whole that we see the gaps in our knowledge and learn the direction which our investigations must take in the future. May the attempts at this structure ever be renewed. No one who works at it but adds something to our knowledge.' "*
>
> Ludwig Edinger (1891)

Every now and then science generates an idea that is widely viewed as profane or seditious—a view of the relationship between humans and the rest of the universe that subverts time-honored cultural traditions and yet in the long run is supported by the facts. The first great intellectual revolution along these lines, which has finally been won, was started in 1543 by the Polish astronomer and physician, Nicolaus Copernicus (1473–1543). In his book, *De Revolutionibus*, which was published in the year he died, a fundamental conclusion was that humans do not occupy a place at the center of the universe, as Aristotle and the Bible stated or at least seemed to indicate, respectively. Instead, we merely reside on a planet that circles round the sun. The latest revolution, which began in 1859 and is still being debated in the public's mind, was sparked by *The Origin of Species* by Charles Darwin (1809–1882). As we know, the immortal English naturalist had the courage to argue with dignity and force that humans are not the products of special creation, but instead are the products of "chance" evolution from "lower" animals over an unimaginably long period of time.

In Chapter 2 we noted that the seeds of evolutionary thinking can be traced back to antiquity. For example, Aristotle recognized that the great diversity of life forms can be accounted for by a small number of fundamental body plans, each with many variations on a common theme. However, this did not extend to thinking about you and me, and one can only imagine the impact that the drawing shown in Figure **5.1** had on the reflective public when Pierre Belon (1517–1564) published it in 1555. He is considered by many to be the founder of modern comparative anatomy—the first great practitioner of that science since Aristotle—and he had the brilliant insight to render the bird skeleton at the same scale as the human skeleton, driving home his basic insight that the skeleton of the two is essentially homologous. What does this mean?

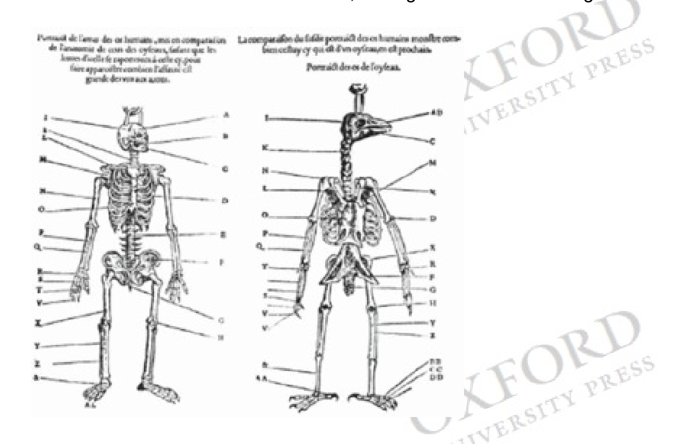
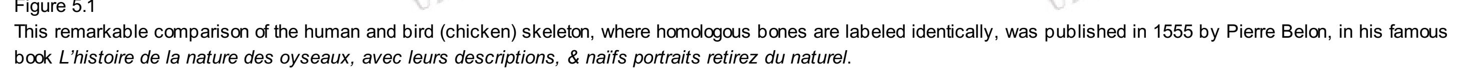


Figure 5.1
This remarkable comparison of the human and bird (chicken) skeleton, where homologous bones are labeled identically, was published in 1555 by Pierre Belon, in his famous book *L'histoire de la nature des oyseaux, avec leurs descriptions, & naïfs portraits retirez du naturel.*



Simple observation reveals that the bones of the head, neck, trunk, upper limbs (wings in birds, arms in humans), and lower limbs are striking similar if one ignores details of length, thickness, and exact shape. In other words, the *topology* of the parts—their relationship to each other—is basically the same in birds and humans, although the precise

geometry (*topography*) of individual parts, and the overall geometrical appearance of the assembly, may be different. If one accepts this principle, it doesn't take much imagination to postulate that the muscular system of birds and humans (a mammal) is also homologous in basic organization, simply because muscles are attached to and move the skeleton. In fact, it might be reasonable to postulate that all of the great systems of the body—including the nervous system—may share a common fundamental architecture.

Results emerging from centuries of biological research after Belon have led to the broad generalization that the entire Vertebrate subphylum of Chordates (which includes fish, amphibians, reptiles and birds, and mammals) has the fundamental body plan shown in Figure **5.2**. At the core, this body plan includes four elements that are displayed at some time during the life cycle of all of them. First, there is a notochord, which is a stiff cartilaginous rod that extends along the midline of the body, preventing it from shortening or bending excessively during locomotion (for example, swimming), which is a very efficient arrangement. Second, there is a dorsal central nervous system, which is hollow and consists of a large brain in the head and a thinner spinal cord extending down the trunk. Recall that invertebrates have a condensed ventral nerve cord, and no notochord (Chapter 4). Third, vertebrates have a series of pharyngeal or branchial arches (paired gill slits in fish and amphibians; also see Fig. **5.4**) for respiration and feeding that are associated with a ventral, unidirectional digestive system (which starts in the mouth and ends in the anus, or cloaca). And fourth, vertebrates have segmented skeletal muscles along the body, and in a postanal tail. Early in evolution virtually all of the skeletal muscle is used for swimming, but in land animals the limbs and head become much more differentiated and mobile.

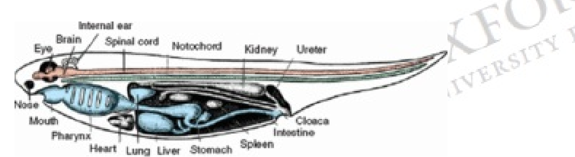


Figure 5.2
The basic vertebrate body plan. The central nervous system (brain and spinal cord) is in light red, the notochord in light green, and the digestive system in light blue in this schematic view. Adapted with permission of Elsevier from A.S. Romer, *The Vertebrate Body*, fifth edition (Saunders: Philadelphia, 1977, p. 3).

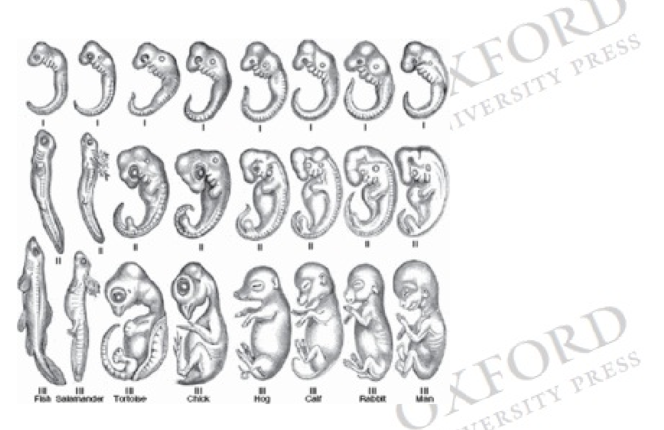


Figure 5.4
Baer's law that in vertebrate embryogenesis the general develops before the specific is nicely illustrated here. Approximately 4-week (I, three brain vesicle), 5-week (II, five brain vesicle), and 8-week (III) human embryos are shown (right column), along with embryos of other species at approximately corresponding stages of development. From G.J. Romanes, *Darwin, and After Darwin* (Open Court: Chicago, 1892, pp. 152–153).

Although less than 0.1% of the animal species on earth today utilize the vertebrate body plan, those that do show by far the most complex, modifiable behavior in the animal kingdom, and they are certainly of greatest interest to us. In the end, humans are really just a specialized vertebrate, and the organization of our nervous system—with its all-important brain—is simply a reflection of how the rest of our body is specialized relative to other vertebrate classes and species. It is a variation on the basic vertebrate plan, and we shall now examine that plan as revealed through the embryological development of the nervous system. The embryo starts out simple (a single cell, the fertilized egg) and becomes more differentiated over time, just as the nervous system underwent progressive differentiation during the course of evolution (see Chapters 3 and 4). This is a venerable approach in biology—the comparison of *ontogeny* (individual development) and *phylogeny* (species evolutionary history)—because each approach proceeds from simple to complex with a number of interesting parallels.

Embryological Perspectives

As we saw in Chapter 2, Aristotle realized that the embryo would reveal the fundamental body plan as one follows over time its progressive differentiation and specialization. It goes without saying that he did not have at his disposal the tools needed (like a microscope) to carry this line of research very far. Aristotle's first great successor in this arena was the Italian anatomist Marcello Malpighi (1628–1694), a Fellow of the Royal Society of London and physician to the Pope. His embryological masterpieces on the chick embryo were published in the mature phase of his career, in 1673 and 1675. For this research he used simple compound microscopes, and he discovered that the earliest recognizable shape of the nervous system is a regionalized, spoon-shaped plate, which is followed by a stage with three longitudinally arranged swellings in the brain region, and then a stage with five longitudinally arranged swellings in the brain region (Fig. **5.3**). At the earlier, *neural plate*, stage the broad region is near the rostral end of the embryo and corresponds to the future brain, whereas the narrower stem lies more caudally and corresponds to the future spinal cord. Malpighi noted that whereas the brain region goes on to form a series of swellings, the spinal cord region retains a simpler, smoother, narrower shape.

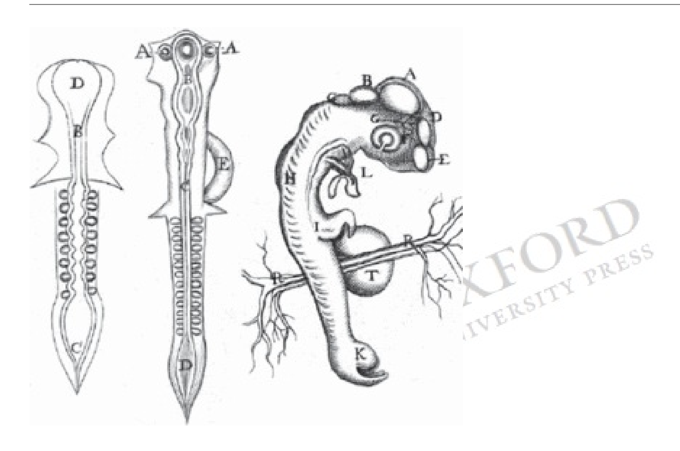




Figure 5.3
These three drawings by Marcello Malpighi were published in 1675 and illustrate early development of the chick central nervous system. In the drawing on the left, the embryo has been straightened out and flattened to display critical features more clearly. It shows the neural plate with prospective brain (D) and spinal cord (B) regions, and below (caudal to) that an indication of eight pairs of somites. The middle drawing shows the three primary brain vesicle stage of the neural tube (B) and the eyes (A). The drawing on the right shows the five secondary brain vesicle stage that develops into the endbrain (E), interbrain (D), optic cup and choroid fissure (F), midbrain (A), hindbrain (B), and medulla (or afterbrain, C). From M. Malpighi, *Anatome Plantarum. Cui subjungitur Appendix, Iteratas & auctas ejusdem Authoris de Ovo Incubato Observationes continens* (John Martyn: London, 1675, Figs. 16, 19, and 36).

Nothing of any real significance was added to Malpighi's account for a century and a half—until the landmark work of Karl von Baer (1792–1876) was published between 1828 and 1837. Here he provided the first truly full and adequate description of chick development. But much more important he followed this with a masterly elaboration of principles that govern vertebrate development in general. In doing so, he laid out essentially everything we know today about the macroscopic features of development—that is, features not based on the cell theory, which as mentioned earlier was not articulated until 1838–1839, by Schleiden and Schwann.

The story Baer told is fundamental. At an early stage of differentiation, the vertebrate embryo is *trilaminar*—it consists very simply of three stacked sheets that are roughly oval in shape. They are *ectoderm* dorsally, *endoderm* ventrally, and *mesoderm* in the middle. Furthermore, the neural plate is a bilateral, midline differentiation of the ectoderm, the layer that also goes on to form the outer surface (skin) of the animal. During later stages of development the three embryonic ("germ") layers roll into a tube and fuse ventrally, so that the surface ("somatic") ectoderm is on the outside and the endoderm is on the inside, lining the digestive system. The mesoderm goes on later to form bone, muscle, blood vessels, and other tissues.

To state this more formally, Baer identified three broad stages of differentiation in all vertebrate embryos. First there is primary differentiation or formation of three embryonic layers, the trilaminar disc stage, that ends when they in turn form concentric tubes. Next there is secondary, histological differentiation within the layers. And finally there is tertiary, morphological differentiation of primitive organs, most of which he described quite well. In short, Baer showed how the basic plan of the vertebrate body illustrated in Figure **5.2** is constructed from three stacked sheets in the early embryo. His fundamental conclusion, that in embryogenesis general features appear before specialized features, is perfectly captured in an anecdote from the first volume of his masterpiece (1828): "I have two small embryos preserved in alcohol that I forgot to label. I cannot at the moment determine the genus to which they belong. They may be lizards, small birds, or even mammals." Figure **5.4** makes the point graphically and brings new meaning to the adult vertebrate body plan first illustrated by Belon (Fig. **5.1**).

Earliest Stages of Mammalian Development

Let's now return to Baer's stage of primary embryonic differentiation and sketch the fascinating story of how the trilaminar embryonic disc is actually formed in mammals, using the human as a typical example (Fig. **5.5**). The power of this approach lies in its simplicity. After all, the starting point is a single cell, the *fertilized egg*, which has one copy of DNA (the genetic program for development and mature function) from the father's sperm and a different copy from the mother's egg itself. The fertilized egg divides a number of times to form a ball of more or less similar cells known as a *morula*, and then a dramatic event occurs. A large, fluid-filled cavity develops within the morula. This cavity is known as the *blastocyst cavity* (blastocele), and the yolk sac differentiates from it at later stages. On the other hand, the cells themselves are arranged into a thin *outer cell mass* that lines the blastocyst cavity, and a condensed *inner cell mass* that is the future embryo itself. This is called the *blastocyst* stage of development.

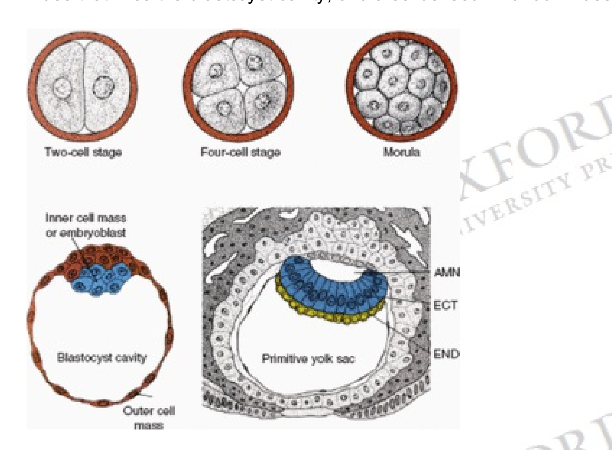


Figure 5.5
Formation of the human bilaminar embryonic disc (lower right) from the two-cell stage (upper left) through the blastocyst stage. The inner cell mass develops during the fourth day after fertilization, and the blastocyst (lower right) is about 9 days old. The blastocyst cavity becomes the primitive yolk sac as a very thin layer of endodermal cells (END) spreads down to coat the inner surface of the blastocyst cavity. Key: AMN, amnionic cavity; ECT, ectoderm. Adapted with permission from T.W. Sadler, *Langman's Medical Embryology*, fifth edition (Williams & Wilkins: Baltimore, 1985, pp. 29, 31, 41).

The next highlight of our story occurs when a second cavity—the *amniotic cavity*—develops within the inner cell mass itself. A remarkable thing happens at this stage. The

part of the inner cell mass between the two cavities becomes organized into two monolayers of cells—like parallel brick walls—the *bilaminar embryonic disc*. The monolayer layer "on top," next to the amniotic cavity, is the ectoderm and it is referred to as dorsal in the embryo. Conversely, the monolayer layer "on the bottom," next to the primitive yolk sac, is the endoderm and it is referred to as ventral in the embryo at this stage of development.

Then comes the single most important event for nervous system formation. To set the stage (Fig. **5.6**), look down on the oval *bilaminar embryonic disc* from above and identify two clear features that divide the ectoderm into right and left halves. Near one end of the disc there is a circular patch where the ectoderm and endoderm appear to be fused or "welded" together, and at the other end there is a groove with a swelling on the end. The circular patch, which helps define the rostral end of the embryonic disc, seems rather boring—it is called the *oropharyngeal membrane* and will become the opening between the mouth and the pharynx (throat), the rostral end of the digestive system. In contrast, the groove and swelling help define the caudal end. They are called the *primitive streak* and *primitive node (of Hensen)*, and they are specialized regions of the midline ectoderm that do something remarkable: they generate cells that pinch off and then migrate between the ectoderm and endoderm to form the mesoderm.

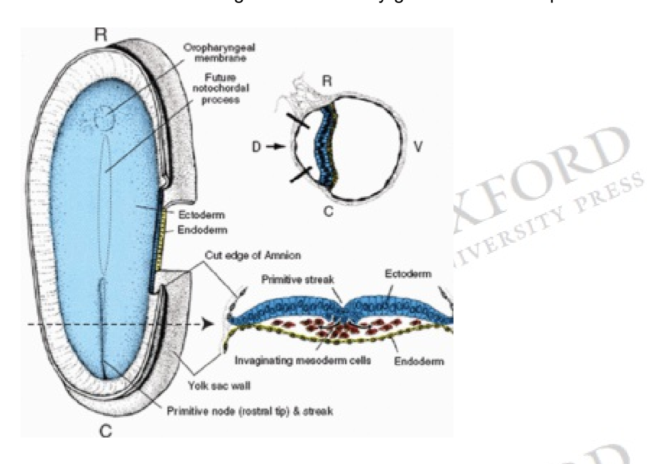


Figure 5.6
Formation of the human trilaminar embryonic disc. The figure on the left is a top or dorsal (D) view of the ectodermal layer (blue) of an approximately 14-day-old human embryo, with the amnion cut off to expose the ectoderm (see orientation at top right of figure; arrow indicates vantage point, with embryonic disc vertical). The oropharyngeal membrane is near the rostral (R) end of the embryonic disc, and the primitive node and streak are near the caudal (C) end of the embryonic disc, which thus has bilateral symmetry (right and left sides). The figure at the bottom right is a transverse section through the dorsal view of the disc in the left half of the figure, at a slightly later stage of development (about 2 days), and shows formation of the mesodermal layer by invagination from the primitive steak. The dashed line through the primitive streak in the figure on the left shows the level of the transverse section. Note that in this scheme the ectoderm is dorsal and the endoderm is ventral (V). So at this very early stage the cardinal rostrocaudal, dorsoventral, and mediolateral axes can be recognized (compare with Fig. 4.1; also see Appendix A). The presumptive location of the notochordal process about 2 days later (Fig. **5.7**) is indicated by the dashed oval in the figure on the left. Adapted with permission from T.W. Sadler, *Langman's Medical Embryology*, fifth edition (Williams & Wilkins: Baltimore, 1985, pp. 48, 49).

The single most important event for nervous system formation is differentiation of the primitive node discovered by Victor Hensen (1835–1924), which Hans Spemann (1869–1941) and Hilde Mangold (1898–1924) showed in the 1920s is a primary "*organizer*" of the nervous system. When the node or organizer is removed, the nervous system fails to develop at all, whereas a transplanted organizer directs the construction of a second, parallel nervous system in an embryo. A molecular genetics explanation of the organizer instructional program is one of the holy grails of neuroscience that remains to be captured, although a rather minute description of cellular events associated with nervous system differentiation has been available for some time.

Early on, cells from the rostral tip of Hensen's node migrate rostrally along the midline, toward the oropharyngeal membrane, which provides a barrier to their further movement. These midline cells, which stretch from Hensen's node to the oropharyngeal membrane as a cigar-shaped mass, become mesoderm that forms the *notochordal process* (Figs. **5.6** and **5.7**). This process is very interesting because the notochordal process in turn forms the notochord, a defining characteristic of vertebrates. But the situation is even more interesting because some factor or combination of factors secreted from notochordal cells then diffuses dorsally to *induce* changes in midline regions of the overlying ectoderm—and these changes actually represent the induction of a dorsal central nervous system, another cardinal feature of vertebrates. The most thoroughly examined candidate factor to date is the protein *sonic hedgehog*, which is the vertebrate homolog of a protein discovered in the fruit fly Drosophila that is involved in segmentation of the body during embryogenesis. As the mammalian embryonic disc (which is now trilaminar because of the mesodermal layer) grows, cells are added to the caudal end of the notochordal process, that is, to the end adjacent to Hensen's node. In other words, the notochordal process grows from rostral to caudal, and the overlying neural ectoderm is induced from rostral to caudal. There is a temporal gradient in neural ectoderm formation, with the rostral end being the oldest and the caudal end the youngest.

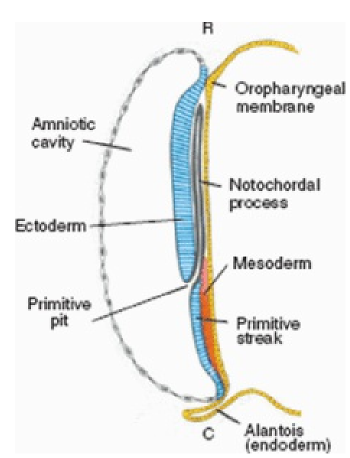


Figure 5.7
Formation of the notochordal process in a roughly 16-day-old human embryo. The notochordal process is a transitory tube-shaped aggregate of mesodermal cells in the median plane of the trilaminar embryonic disc that stretches from the primitive pit (part of the primitive node, Spemann's organizer region) caudally (C) to the oropharyngeal membrane rostrally (R); see Figure **5.6** left. The notochordal process later fuses with the endoderm to form the notochordal plate, and then pinches off to lie between the midline endoderm

and ectoderm as the solid, definitive notochord. Adapted with permission from T.W. Sadler, *Langman's Medical Embryology*, fifth edition (Williams & Wilkins: Baltimore, 1985, p. 49).

Neural Plate: Central Nervous System Divisions

Now we can return to the neural plate stage discovered by Malpighi (Fig. **5.3** left) and describe its fate in cellular terms. To begin with, the inductive influence of the notochord (Fig. **5.7** legend) is responsible at least in part for differentiating the ectoderm into a central, spoon-shaped neural ectoderm, and a peripheral somatic ectoderm that goes on to form the skin, as we will see. The two regions are easily distinguished because the neural ectoderm is thicker than the somatic ectoderm—when examined in cross-section, cells in the neural ectoderm are taller than those in the somatic ectoderm and this is why the neural plate is easy to see macroscopically (Figs. **5.8** top and **5.9**b). As mentioned several times already, the bowl of the spoon (which is rostral and formed earliest) is the presumptive brain, whereas the handle (which is caudal and formed later) is the presumptive spinal cord, although there is no clear borderline or histological distinction between the two at this stage. In addition, a *neural groove* extends down the midline and separates the plate into right and left halves called *neural folds*.

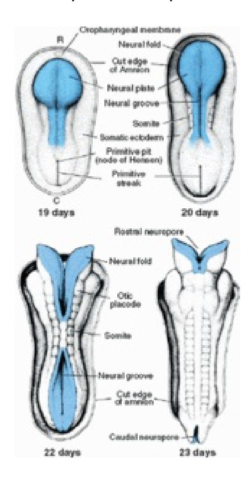





Figure 5.8
Formation of the human neural tube from the neural plate—neurulation—is shown here from a dorsal perspective in a series of embryos from about 19 to 23 days after conception. Note that initial closure of the tube (about 22 days) takes place in roughly the future neck region of the embryo, and then proceeds in both a rostral (R) and a caudal (C) direction. The process of neurulation in transverse section (A on day 19, A–E on day 22) is shown in Figure **5.11**. Adapted with permission from T.W. Sadler, *Langman's Medical Embryology*, fifth edition (Williams & Wilkins: Baltimore, 1985, pp. 335, 336).

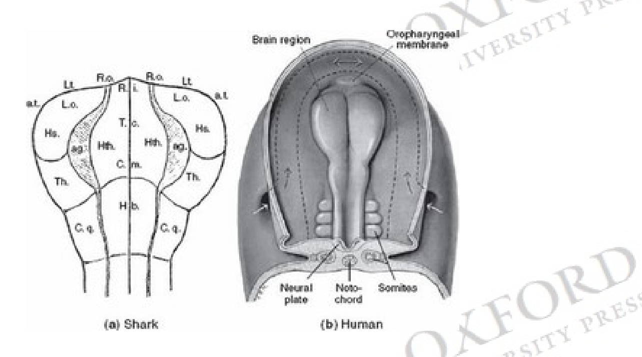


Figure 5.9
Dorsal views of the neural plate in young shark *(a)* and human *(b)* embryos. The notation in *(a)* indicates Wilhelm His's fate map of the shark neural plate; the embryo in *(b)* is about 3 weeks old. Key: Ag., optic stalk; A.t., terminal angle; C.m., mammillary body (of hypothalamus); C.q., quadrigeminal body (tectum); Hb., "tegmental" eminence (tegmentum); Hs., pallial hemisphere (cerebral hemisphere); Hth., hypothalamus; L.o., olfactory lobe; L.t., terminal lamina; R.i., infundibular recess; R.o., optic recess; T.c., tuber cinereum; Th., thalamus; with the optic chiasm falling between the infundibular and optic recesses. View (*a*) from W. His, *Arch. Anat. Physiol.* Leipzig, Anat. Abth., 1893, [no vol.], p. 169. View (*b*) adapted from W.J. Hamilton and H.W. Mossman, *Human Embryology*, fourth edition (Williams & Wilkins: Baltimore, 1972, p. 77).

In short, we have a polarized (rostrocaudal), bilaterally symmetrical, regionalized sheet of cells that represents the future central nervous system, with its brain and spinal cord divisions. The sheet is a monolayer of progenitor or stem cells that divide over and over to produce more progenitor cells at an exponential rate. The differentiation of neurons occurs later, as we shall soon see.

Put another way, the architecture of *the central nervous system* at its earliest stages of development is incredibly simple. Topologically, it is *a flat, bilaterally symmetrical sheet that is one cell thick*. Naturally, there has been great interest in determining whether any of the later regional divisions of the nervous system can be detected in the neural plate. The first, and probably most insightful, attack on this problem was carried out by Wilhelm His (1831–1904), the greatest neuroembryologist of the nineteenth century. In examining his vast collection of vertebrate embryos, he believed that the shark neural plate displays enough features to distinguish the major divisions observed in the brain of other, more advanced, vertebrates at later stages of development (Fig. **5.9**a). In this model, the rostral end of the early neural plate is at the level of the infundibulum—the stalk of the pituitary gland that develops in the midline, just at the level of the oropharyngeal membrane. Also note that His identified a series of transverse and longitudinal divisions or parts of the shark neural plate. How might this apply to nervous system development in mammals?

A schematic view of the mammalian neural plate and other differentiations of the ectoderm is shown in Figure **5.10**, along with an indication of where certain major features appearing at later stages of development are probably located. This is a *fate map* of the neural plate, and it is based on currently available evidence from the study of normal embryological development (like the work of His just mentioned) and experimental analysis of developmental mechanisms. Note that at this early stage of neural plate formation the hypophysial placode, which forms part of the pituitary gland and its stalk, lies between the oropharyngeal membrane and the rostral tip of the neural plate, just as in His's model (Fig. **5.9**a).

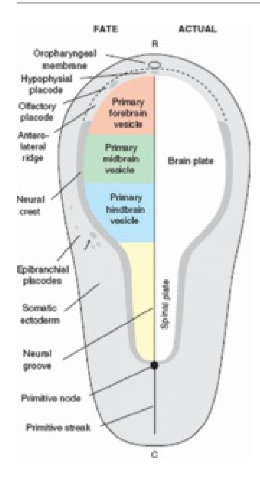






Figure 5.10
A simple fate map of the human ectodermal layer, including the neural plate (compare with Fig. **5.8**, upper left). The actual structures visible at this stage are shown on the right side; those evident in the upcoming three primary vesicle stage of neural tube development (Figs. **5.12** and **5.13**) are shown on the left. The hypophysial placode generates Rathke's pouch, which goes on to form the anterior and intermediate lobes of the pituitary gland; the olfactory placode generates the sensory neurons of the olfactory mucosa. The anterolateral ridge is a poorly defined rostral extension of the neural crest. The arrow in the epibranchial placodes indicates the otic placode, which generates the membranous labyrinth of the inner ear. The gently curving ectoderm has been flattened for clarity. Key: R, rostral; C, caudal. Adapted with permission from L.W. Swanson, The architecture of nervous systems, in: L.R. Squire, *Fundamental Neuroscience*, third edition (Academic Press: San Diego, 2008, p. 24).

Nowadays, there is intense interest in characterizing regionalized patterns of gene expression in the mammalian neural plate. Such patterns might suggest molecular mechanisms for regionalization of the neural plate, and thus regional differentiation of neuroectodermal cells, before the actual production of neurons themselves, and even before the neural tube is formed. Such patterns are beginning to surface, although their significance is still fairly obscure, partly because their relationships to the morphological features just mentioned are not entirely clear. We can expect great progress here in the very near future.

Neural Tube: Transverse Brain Divisions

Everyone knows that the brain and spinal cord are inside the body, not on the surface. How does the ectodermal neural plate end up forming the internalized central nervous system? The answer is that, in essence, the walls of the neural plate (the neural folds) assume a vertical orientation, the dorsal lips fuse, and the resulting tube sinks into the body, between the dorsal ectoderm (future skin of the back) and the notochord (Fig. **5.11**a–c). This process of turning the neural plate into the neural tube is called *neurulation*. In mammals, the dorsal fusion tends to start near the transition between brain and spinal cord, basically in the future neck region, and then extends both rostrally and caudally until a closed tube is formed (Figs. **5.8** and **5.11** left). From a topological point of view, it is important to note that the midline of the neural plate becomes the ventral midline of the neural tube, whereas the lateral margins of the neural plate become the dorsal midline of the neural tube.

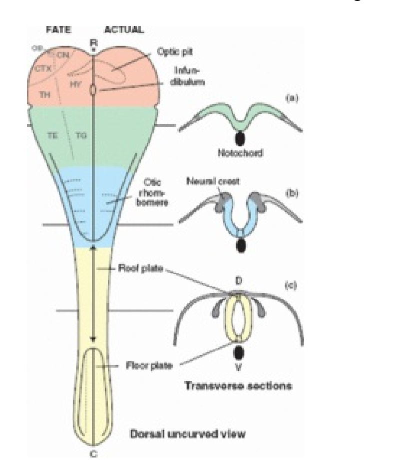




Figure 5.11
Left. Actual regionalization of neural ectoderm just as the neural plate is beginning to form the neural tube is shown on the right half of the neural tube-plate (compare with Fig. **5.8** lower left; and Fig. **5.10** where the color coding is the same). The first obvious feature to appear is probably the otic rhombomere (also see nearby otic placode in Fig. **5.8** lower left, and arrow in Fig. **5.10** associated with epibranchial placodes), which divides the prospective primary hindbrain vesicle region into three sequential primary rhombomeres (prorhombomeres). Shortly thereafter two features are detectable in the prospective primary forebrain vesicle region: the optic pits, which are continuous across the midline, and just caudal to them the midline infundibulum, which will form the posterior lobe of the pituitary gland. On the left side of this drawing major features that will appear in the five secondary brain vesicle stage of development are indicated as a fate map, separated by grooves identified in Figure **5.14**. *Right*. Three stages of neurulation shown in transverse sections of the same embryo at different rostrocaudal (R-C) levels. Note that the neural groove of the neural plate becomes incorporated into the floor plate of the neural tube, and that it lies ventrally (V). The lateral edge of the neural plate, adjacent to the neural crest and anterolateral ridge, becomes associated with the roof plate of the neural tube, which lies dorsally (D). Key: *, terminal lamina (lamina terminalis); CN, cerebral nuclei; CTX, cerebral cortex; HY, hypothalamus; TE, tectum; TG, tegmentum; TH, thalamus. Adapted with permission from L.W. Swanson, The architecture of nervous systems, in: L.R. Squire, *Fundamental Neuroscience*, third edition (Academic Press: San Diego, 2008, p. 25).

In mammals, the first two structural differentiations of the neural plate that can be identified with certainty are in the brain division at just about the stage where the neural tube begins to form (Fig. **5.8** lower left and Fig. **5.11**). They include a rostral region that goes on to form the retinas and optic nerves (the optic pits and optic vesicles) and a caudal region that is associated with the inner ear (the otic rhombomere). Somewhat later, there is some evidence to suggest that a midbrain region of the neural plate can be seen, which would imply that the region of the plate rostral to it will—as we will now see—go on to form the primary forebrain vesicle and the region caudal to it the primary hindbrain vesicle.

At the stage when the brain region of the neural tube is finally completely closed at the rostral end, it displays three rather distinct swellings or vesicles (Figs. **5.12** and **5.13** right), just as Malpighi first illustrated. Therefore, it should come as no great surprise that at least hints of these three vesicles should be detected in the preceding stage of neural plate growth (Fig. **5.11**). Baer provided a great practical service to neuroanatomy when he gave simple, clear names (originally in German) to these rostrocaudally arranged transverse swellings: primary forebrain vesicle, primary midbrain vesicle, and primary hindbrain vesicle. The earlier nomenclature starting with Malpighi was based on attempts to apply the names of poorly understood adult parts to the early neural tube, and this led to profound confusion. Today, Baer's names and interpretation form the cornerstone of regional or topographic neuroanatomical nomenclature, as a glance at the table of contents of most neuroanatomy textbooks published in the last century shows. He suggested that there are *three primary brain vesicles*, which go on to subdivide into a series of *five secondary brain vesicles* that in turn form the five basic topographic divisions of the adult vertebrate brain. In this scheme, the retinal region is in the primary forebrain vesicle and the otic region is in the primary hindbrain vesicle.

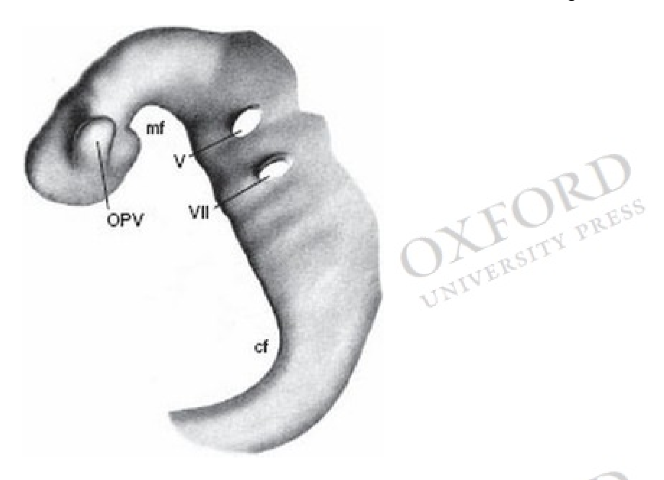




Figure 5.12
The outer surface of the neural tube at the early three primary brain vesicle stage. This lateral view of the left side of a model of the neural tube in a 4.8 mm long human embryo shows the very clear optic vesicle (OPV) evaginating from the primary forebrain vesicle, the midbrain flexure (mf) and cervical flexure (cf), and the sites of the trigeminal (V) and facial (VII) cranial nerves. An interpretation of regionalization in mammalian embryos at this stage is shown in Figure **5.13**. From F. Hochstetter, *Beiträge zur Entwicklungsgeschichte des menschlichen Gehirns. I. Teil*. (Deuticke: Vienna, 1919, Table 1, Fig. **4**).

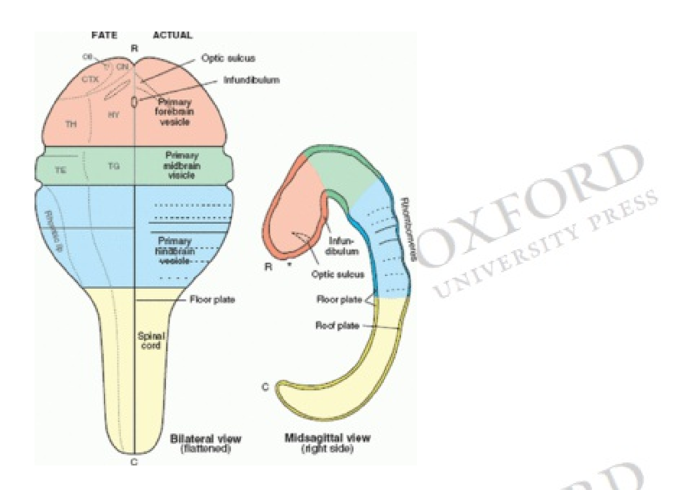




Figure 5.13
Right. This view of the right side of a bisected neural tube with three primary brain vesicles is a schematic interpretation of the model shown in Figure **5.12** (which shows the outer surface of the left or removed side). The main advance from the preceding stage (Fig. **5.11**) is differentiation in the primary hindbrain vesicle of seven or eight definitive or secondary rhombomeres, with the otic rhombomere being number 4—counting from rostral (R) to caudal (C). Key: asterisk indicates approximate location of rostral neuropore closure (see Fig. **5.8** lower right). *Left*. A conceptual flat map of the three primary brain vesicle neural tube, produced in principle by cutting the roof plate and laying the walls of the neural tube down flat (like opening a book), so that the ventral midline (floor plate) forms the midline longitudinal axis, dividing the map into right and left halves. As in Figures **5.10** and **5.11**, the right half shows actual features observed at this stage, whereas the left half shows the presumed location of features that will appear later in development. Compare the overall shape with that in Figure **5.10**. Adapted with permission from L.W. Swanson, The architecture of nervous systems, in: L.R. Squire, *Fundamental Neuroscience*, third edition (Academic Press: San Diego, 2008, p. 26).

The five secondary brain vesicle stage of the neural tube arises from subdivision of the primary forebrain and hindbrain vesicles (Fig. **5.14**). When viewed from above or below, the primary hindbrain vesicle becomes roughly diamond shaped (hence the adult *rhombicbrain* or rhombencephalon), with the rostral half going on to form the (*secondary*) *hindbrain* (epencephalon, with its adult pons and cerebellum) and the caudal half forming the *afterbrain* (metencephalon, usually called medulla). Differentiation of the forebrain vesicle is a bit more complex, although in essence a deep groove (when viewed from the outside; the hemispheric sulcus) forms rostrodorsally on the right and left sides to produce the right and left *endbrain* at the rostral and dorsal end of the neural tube, followed by and attached to the unitary *interbrain*. The endbrain (or telencephalon) is also called the cerebral hemisphere (or just cerebrum), whereas the interbrain is also known as the diencephalon, and the neuroepithelial patch that generates the retina and optic nerves lies within it.

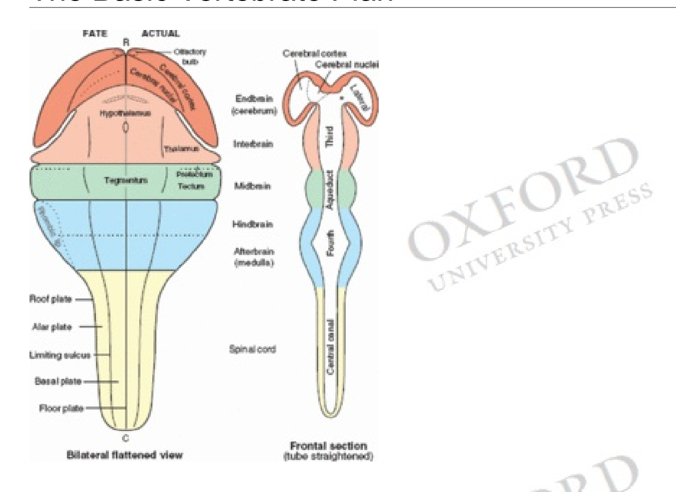


Figure 5.14
Right. Conceptual view of the five secondary brain vesicle stage of neural tube development. It is a frontal (longitudinal) view of the straightened out neural tube, where the walls are color-coded to indicate vesicle identity and the lumen becomes the cerebral ventricles, with the names of the adult segments indicated. *Left*. A conceptual flat map of the early neural tube with five secondary brain vesicles, produced like that in Figure **5.13** left. As in earlier figures of this series, the right half shows actual features observed at this stage, whereas the left half shows the presumed location of features that will appear later in development. The five-vesicle stage goes on to form the five major topographic divisions of the adult vertebrate brain; the primary hindbrain vesicle forms the adult rhombicbrain, with the rostral half becoming the (secondary) hindbrain (with the adult pons and cerebellum) and the caudal half becoming the afterbrain (usually called the medulla). Adapted with permission from L.W. Swanson, The architecture of nervous systems, in: L.R. Squire, *Fundamental Neuroscience*, third edition (Academic Press: San Diego, 2008, p. 26).

To recapitulate, at the earliest stage of neural tube differentiation, there are three transverse swellings that are arranged from rostral to caudal—the primary forebrain, midbrain, and hindbrain vesicles. Then, at the next stage the primary forebrain and hindbrain swellings divide again so that now we have six rostrocaudally arranged secondary vesicles that go on to form the five major topographic divisions of the adult brain—endbrain (right and left), interbrain, midbrain, hindbrain, and afterbrain (medulla), which of course is followed by the spinal cord. Amazingly enough, the wall of the early five vesicle-stage neural tube is still a monolayer neural epithelium formed entirely by stem cells; no neurons have been born yet, although regionalized gene expression patterns are seen.

The early neural tube has an obvious segmented appearance, which is even easier to appreciate if the tube is artificially straightened out and sliced frontally (Fig. **5.14** right). Late nineteenth-century embryologists referred to these transverse differentiations as *neuromeres*, and it is still not clear whether they are segments (metameres) in the true sense of serial homologous units formed by a common program of gene expression, or whether they are simply unique regionalizations. In any event, they have received a great deal of attention, and it now seems clear that they are *proliferation zones* for neurogenesis. A series of transitory neuromeres in the primary hindbrain vesicle (which becomes the rhombicbrain), the *rhombomeres*, are especially intriguing and appear to be related to early differentiation of the cranial nerve nuclei and the adjacent gill slits—another core vertebrate feature also known as pharyngeal or branchial arches in birds and mammals. The presence and identity of "segments" in the midbrain (*mesomeres*) and forebrain (*prosomeres*) remains confusing and unsettled.

Neural Crest and Placodes: Peripheral Nervous System

The neural plate represents the central nervous system, with its brain and spinal cord topographic divisions. However, there is a narrow "transition zone" between the neural plate and the somatic ectoderm that pinches off when the neural tube separates from the surface ectoderm and sinks into the interior of the embryonic body (Figs. **5.10** and **5.11**a–c). This intermediate strip of ectoderm, the *neural crest*, goes on to form (among other things) most of the ganglia of the *peripheral nervous system*. After pinching off from the ectodermal layer, neural crest cells migrate ventrally into the developing body for greater or lesser distances (Fig. **5.15**). As a broad generalization, the neural crest cells that remain closest to the neural tube form the *sensory ganglia*, while those that migrate the farthest end up constituting the *autonomic ganglia*.

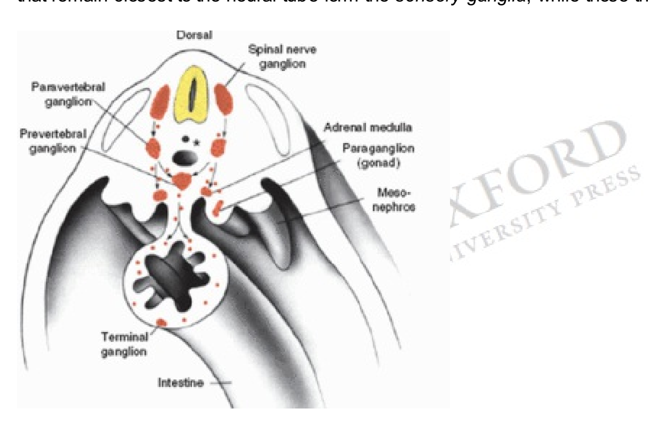


Figure 5.15
Ventral migration of neural crest cells (red) from their early position on either side of the neural tube (yellow) down into the viscera. This is a transverse section through abdominal levels of a schematic mammalian embryo after the neural crest has pinched off from the neural tube (see Fig. **5.11**c, where the primordial spinal ganglion is shown in gray). The asterisk indicates two features: the notochord (dorsally) and the aorta (ventrally). Adapted with permission from M.B. Carpenter and J. Sutin, *Human Neuroanatomy*, eighth edition (Williams & Wilkins: Baltimore, 1983, p. 69).

Pairs of sensory ganglia are arranged more or less regularly along the right and left sides of the rhombicbrain and spinal cord. As the name implies, they are collections of sensory neurons that transmit information from various parts of the body (skin, muscle, blood vessels, viscera, and so on) to the central nervous system (Chapter 11). The extensions of sensory ganglion cells form important components of the cranial and spinal nerves. In his first publication as a young medical student in 1877, Sigmund Freud (1856–1939) made the interesting discovery that in the most primitive vertebrates (lamprey) sensory ganglion cells are found within the spinal cord, as well as in sensory ganglia adjacent to the cord. Some 14 years later the great Swedish neuroanatomist Gustav Retzius (1842–1919) discovered that in an even more primitive animal, amphioxus

(which is in the subphylum Cephalochordata), all sensory "ganglion" cells are found in the spinal cord; and we now know that there is even a sensory ganglion in the midbrain of mammals (the midbrain trigeminal nucleus).

Autonomic ganglia are actually collections of motor neurons that innervate the viscera. Their distribution, and the organization of their connections, is exceptionally complex and poorly understood. Broadly speaking, they fall into two functionally distinct subsystems: sympathetic and parasympathetic (discussed in Chapter 8). They are responsible for the largely involuntary or unconscious motor control of the viscera during both sleep and wakefulness, and axons entering and leaving them are fundamental components of the peripheral nerves. Like sensory ganglia, autonomic ganglia are associated with both the spinal and cranial nerves.

The wall of the digestive system has an especially extensive differentiation of autonomic nerves and ganglia that is concentrated in three concentric, interconnected layers: the outer myenteric plexus of Auerbach, the middle submucosal plexus of Meissner, and the inner mucosal plexus. It is a vast network (with about as many neurons as the spinal cord) and it displays intrinsic activity that is responsible for generating peristaltic waves and many other activities in the digestive system—and its activity is modulated by inputs from the central nervous system. As mentioned in Chapter 3, these plexuses in the wall of the digestive system seem to display many of the features of a complex nerve net.

For the sake of completeness, one other feature of nervous system development needs to be mentioned—*sensory placodes*. They are tiny patches or islands of ectoderm that lie outside the classic neural plate and crest and are specialized to generate sensory neurons. Two types of sensory placode have been identified (see Fig. **5.10**). One consists of a series of about five placodes laterally adjacent to the primary hindbrain segment of the neural crest. These epibranchial placodes (near the branchial arches) either generate or contribute to the sensory ganglia of cranial nerves V (trigeminal), VII (intermediate nerve), VIII (vestibulocochlear; the otic placode), IX (glossopharyngeal), and X (vagus). The other consists of the *olfactory placode*, which lies near the prospective endbrain region of the neural plate and generates olfactory sensory neurons (cranial nerve I).

Overview

The entire vertebrate nervous system is derived from the embryonic ectodermal layer that also generates the skin, which faces the external environment. The notochord induces differentiation of the neural ectoderm, which forms a spoon-shaped neural plate, with a broader brain region facing rostrally and a narrower spinal cord region facing caudally. The bilaterally symmetrical neural plate is a monolayer of nervous system stem cells that is separated from the somatic ectoderm by a narrow transition zone of ectoderm called the neural crest and anterolateral ridge. As development progresses, the neural plate invaginates into the middle or mesodermal layer of the embryo and then pinches off to form the neural tube, which goes on to form the neurons of the central nervous system. The neural crest also pinches off and migrates down the sides of the neural tube to form sensory and motor neurons of the peripheral nervous system. Other sensory neurons of the peripheral nervous system are derived from a small set of placodes—islands of specially differentiated somatic ectoderm.

In its first stage of development, the rostral half of the neural tube shows three sequential swellings or neuromeres, the primary forebrain, midbrain, and hindbrain vesicles, whereas the caudal half of the neural tube remains relatively simple and forms the presumptive spinal cord. In the next stage of development the three primary brain vesicles transform into five secondary brain vesicles that go on to form the five major topographic divisions of the adult brain: right and left endbrain attached caudally to the unpaired interbrain, midbrain, (secondary) hindbrain, and afterbrain (medulla), followed by the spinal cord. At the earliest stage of the five-vesicle neural tube no neurons have been formed from the wall of the neural tube (the neural epithelium), but this does not last long. Neurogenesis soon begins, and with it a series of longitudinal grooves appear along the inner surface of the wall of the neural tube. This longitudinal differentiation of the neural tube is associated with specific proliferation zones in the neuroepithelium, and their development is the subject of Chapter 6.

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Brain Architecture (2 ed.): Understanding the Basic Plan

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Neurogenesis: Longitudinal Divisions, Parts List, and Adult Flatmap

Chapter: Neurogenesis
Author(s): Larry W. Swanson
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> *"He who can properly define and divide is to be considered a god."*
>
> Plato
>
> *"Regardless of how [scientific] terms are defined by lexicographers or committees of experts, terms cannot be used outside a theory."*
>
> Marcus Jacobson (1993)

We have just seen that early in vertebrate neural tube development a series of five transverse swellings or vesicles that are arranged from rostral to caudal appears in the brain division while the spinal cord division continues to look more like a simple tube with a smaller diameter. Almost immediately, however, a fundamental transformation occurs. The single cell–thick wall of the neural tube begins to generate a distinctive second layer of cells called *young neurons*. Interestingly, throughout the spinal cord and rhombicbrain this process of *neurogenesis* begins ventrally (in the midbrain and forebrain it begins mid-dorsoventrally), which leads to a series of longitudinal grooves along the tube's inner wall. So, as the neural tube grows and differentiates, its wall is divided by a series of outer transverse and inner longitudinal grooves into a patchwork of *neuronal proliferation zones* that go on to form the basic *gray matter regions* of the mature central nervous system.

We will now explore this regionalization and some of its basic consequences, which are both structural and functional—and of great theoretical interest. On the one hand, this developmental regionalization provides the framework for a systematic account of vertebrate central nervous system structure. What are the basic parts, what is their cellular organization, and how are they arranged topographically? This is like geography, and it provides an internally consistent terminology for describing the physical structure of the central nervous system at all stages of the life cycle, in health and in disease. It is the topic of this chapter, which closes the first half of the book and leads into the second half: how the parts are interconnected as a functional system to control behavior and the internal state of the body.

Generating Neuron Types: Longitudinal Central Nervous System Divisions

When the neural tube has differentiated just enough to recognize five brain vesicles and the spinal cord, its wall is still one cell thick, despite an intriguing pseudostratified appearance (Fig. **6.1**). This soon changes, however, and what happens during the transformation provides fundamental insights into the basic plan of the central nervous system that Wilhelm His described so beautifully.

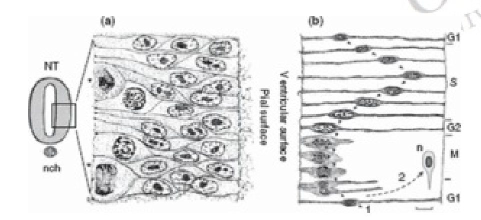


Figure 6.1
Cellular organization of the early neural tube wall is pseudostratified. (*a*) Viewed with a microscope the early neural tube wall (compare with Fig. 5.11*c*) looks like it is three or four cells thick, with cell divisions (*) taking place near the ventricular or luminal surface. Key: NT, neural tube; nch, notochord. Adapted with permission from T.W. Sadler, *Langman's Medical Embryology*, fifth edition (Williams & Wilkins: Baltimore, 1985, p. 338). (*b*) Experimental work showed that the early neural tube wall is actually not stratified, but instead is only one cell thick. The layered appearance is due to up and down "elevator" movements of the nucleus in individual neuroectodermal stem cells, with different phases of the cell cycle occurring at different depths in the neural tube wall (one cell is shown here, with time on the vertical axis). Mitosis (M) occurs near the ventricular surface, DNA synthesis (S) occurs in the outer two-thirds, and the first and second growth phases (G1, G2, respectively) occur in the inner third. After a neuroectodermal stem cell divides, one of two things can happen. First (1), both daughter cells can undergo another round of mitosis, a fate called symmetrical cell division. Second (2), one daughter cell may undergo another round of mitosis, whereas the other becomes a young neuron (n), never to divide again—a fate called asymmetrical cell division. In summary, at the stage illustrated in (a) the neural tube wall is a germinative zone formed by one cell type: dividing neuroectodermal stem cells. Scale bar = 10 μm, chick embryo. Adapted with permission from M. Jacobson, *Developmental Neurobiology* (Holt, Rinehart and Winston: New York, 1970, p. 7) with information from S. Fujita,

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The process is especially clear in the spinal cord segment of the neural tube. When viewed in transverse section (Fig. **6.2**), the early spinal cord presents four clear parts. There is a thin wedge-shaped *roof plate* in the dorsal midline, a thin wedge-shaped *floor plate* in the ventral midline, and two thicker walls, one on the right side and one on the left. At a specific developmental stage certain neuroepithelial stem cells stop dividing and *migrate* out of the generative layer (called the *ventricular* or *ependymal layer*, of the right and left sides) to form a new zone that is referred to as the *intermediate* or *mantle layer* of the neural tube on the right and left sides (Figs. **6.1**-*b2* and **6.2**). These cells have undergone an irreversible developmental process called *determination*, and they will never divide again. They are *young neurons*. Note that the mantle layer of young neurons is sandwiched between two other layers—the inner ventricular layer (which retains a pseudostratified appearance for some time and lines the fluid-filled center of the neural tube, the future *cerebral ventricles* of the adult) and the outer *marginal layer*, which is a relatively cell-free zone near the pial (outer) surface and contains the cytoplasmic extensions of various cell types.

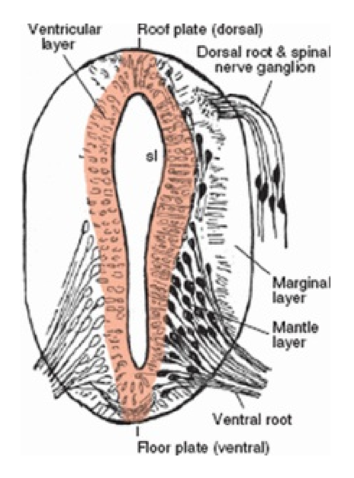






Figure 6.2
The four basic regions and three basic layers of the early neural tube. This composite drawing shows a transverse section of the spinal cord from a human embryo of 4 weeks, combined with the appearance of a spinal nerve ganglion from a human embryo of 4.5 weeks. Note at the latter stage the simple bipolar shape of spinal nerve ganglion cells, each with a dendrite extending toward the periphery and an axon extending into the neural tube. The four regions are the roof plate dorsally and the floor plate ventrally, along with a right and left wall of the neural tube. The three basic concentric layers are the internal ventricular layer (light red), which is the proliferative or germinal zone; the mantle layer, which contains post-mitotic young neurons and becomes highly differentiated later in development; and the marginal layer, which contains few neuron cell bodies but instead mostly cellular extensions. Note that the mantle layer is formed first and thus is thicker ventrally, which results in a thinner ventricular layer. In contrast, the dorsal ventricular layer is thicker, whereas its mantle layer is thinner. This condition leads to a structural feature called the limiting sulcus (sl, *sulcus limitans* in Latin) that basically divides the right and left walls of the neural tube into dorsal and ventral domains. Adapted from L. Edinger (1891) *Twelve Lectures on the Structure of the Central Nervous System* (Philadelphia: Davis, p. 19), which was based on the work of Wilhelm His.

But the deceptively simple drawing in Figure **6.2** reveals much more. On closer inspection it is obvious that the mantle layer at this early stage of development is thicker ventrally than dorsally. In fact, neurogenesis begins ventrally and gradually spreads dorsally—there is a ventral to dorsal gradient of neuron generation in the spinal cord (and, as we shall see, in the rhombicbrain as well). As a result, the ventricular layer is thinner, and the mantle layer is thicker, ventrally. This arrangement causes a shallow groove to appear on the inner wall of the neural tube. Wilhelm His named this longitudinal groove the *limiting sulcus* and pointed out that it roughly divides the right wall and left wall of the early neural tube (in spinal cord and rhombicbrain) into a ventral *basal plate* and a dorsal *alar plate*.

The fundamental significance of the early basal and alar plates was immediately obvious to His. The first neurons to be generated in the neural tube are motor neurons, and their axons grow out of the neural tube in bundles called ventral roots (made up of even smaller rootlets). In contrast, the axons of sensory neurons in the spinal nerve ganglia grow into the alar plate, whose neurons do not extend axons into the ventral (or dorsal) roots. Thus, the early *basal plate is associated functionally with the motor system*, whereas the early *alar plate is associated with the sensory system*.

This clear embryological distinction between basal plate-ventral root and alar plate-dorsal root, and its obvious association with distinct functional systems—motor and sensory, respectively—was a brilliant confirmation of what has been called the greatest single discovery in the history of neuroscience, the Bell-Magendie Law. Sherrington considered it second only to Harvey's discovery of the circulation of the blood in the history of physiology. To make a long and regrettable story short, François Magendie (1783–1855) published elegant experimental proof in 1822 that the dorsal roots transmit sensory information, whereas the ventral roots transmit motor information—shattering ancient beliefs that sensory and motor information are transmitted by the same fibers. In essence, this suggested a “circulation” of neural information, into the spinal cord via the dorsal roots and out of the spinal cord via the ventral roots. This was a fundamental part of the thinking that went into the gradual development of modern concepts of the reflex arc (Chapter 7) because sensory and motor functions could be distinguished unequivocally on anatomical as well as physiological grounds. In the years following 1822, Sir Charles Bell (1774–1842) reprinted some of his earlier papers, correspondence, and a private pamphlet, and very selectively enhanced their contents so that he could claim priority for Magendie's discovery.

Generating Gray Matter Regions

As central nervous system differentiation progresses, various specialized regions of the ventricular layer—the proliferation zones mentioned earlier—generate many additional sets of neuron types in a highly stereotyped spatiotemporal pattern, and the young neurons migrate out into the mantle layer along a more or less direct *radial route* (perpendicular to the neural tube surface and along radial glial cells whose cytoplasmic extensions stretch from the inner to the outer surface of the neural tube), or a radial followed by a *tangential route* (parallel to the surface), before settling down to establish synaptic connections. Thus, as embryogenesis progresses, the wall of the neural tube becomes thicker and thicker, and the spinal cord (Fig. **6.3**) along with each of the brain vesicles becomes characteristically differentiated in different, more or less complex ways.

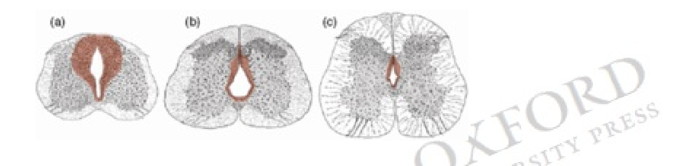




Figure 6.3
Progressive development of the human spinal cord. The histological differentiation of the spinal cord is shown here as drawings from Nissl-stained tissue sections obtained from embryos of roughly (*a*) 7 weeks, (*b*) 8 weeks, and (*c*) 10 weeks of age. The ventricular layer is shaded light red (as in Fig. **6.2**), the intermediate or mantle layer surrounds it on the right and left sides, and it in turn is surrounded on the outside by the marginal layer. Because of the enormous growth of the future gray matter (mantle layer) and future white matter (marginal layer), the lumen of the neural tube (the central canal or spinal part of the ventricles) becomes compressed and also appears to become smaller and smaller. No myelin has formed yet so the central parts of the dorsal and ventral roots are obvious in the marginal layer. Figures are approximately to scale. Slightly adapted from F. Keibel and F.P. Mall, *Manual of Human Embryology*, vol. 2 (Lippincott: Philadelphia, 1910–1912, pp. 49–51).

Nevertheless, even in fully mature adults, the vertebrate central nervous system is, from a topological perspective, nothing more than a closed tube with highly differentiated walls. And it tends to maintain the three concentric layers found in the embryonic neural tube: an *ependymal monolayer* remnant of the ventricular layer that lines the central fluid-filled cavity (the ventricles), a very thick mantle layer of neuron cell bodies (along with glial cells, most of which are generated after the neurons), and a thinner marginal layer of cell extensions and only a few neuron cell bodies. This arrangement is crystal clear in the adult spinal cord (Fig. **6.4**), and more or less evident in most parts of the brain.

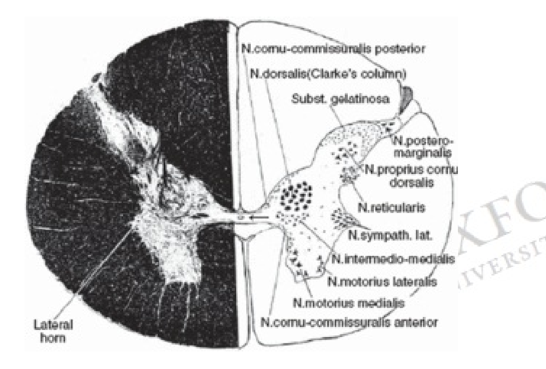




Figure 6.4
Arrangement of white and gray matter in the adult human spinal cord at lower thoracic levels. The left side of the figure shows what the spinal cord looks like in a transverse histological section stained for myelin (with the classical Weigert method). Myelin is black and is arranged around the periphery of the spinal cord, in what was the marginal layer of the embryonic spinal cord (see Figs. **6.2** and **6.3**). The gray matter is unstained (white) but does contain certain myelin-stained tracts that enter or leave the main myelinated regions (funiculi) around the periphery. The right side of the figure is a drawing of major neuronal regionalization observed in the gray matter (as observed with a Nissl stain for neuron cell bodies), in what was the intermediate or mantle layer of the embryonic spinal cord (see Figs. **6.2** and **6.3**). The arrow near the center points to the central canal, which is the tiny (often obliterated) adult remnant of the neural tube's lumen and its ventricular layer, which is now the single-cell-thick ependymal layer. Slightly adapted with permission from O.S. Strong and A. Elwyn, *Human Neuroanatomy* (Baltimore: Williams & Wilkins, 1943, p. 95).

In a very general way, the walls of the adult central nervous system can be divided into what are loosely referred to as *gray matter* and *white matter* because of their appearance to the naked eye when slicing through the brain or spinal cord with a knife. White matter consists of major axon *tracts* that are whitish because thicker axons are surrounded by a myelin sheath that is the product of specialized glial cells, is rich in lipid and thus whitish, and functions to speed up electrical impulses traveling down an axon toward its terminals. However white matter tracts in the central nervous system, and white matter nerves in the peripheral nervous system, contain varying amounts of unmyelinated axons as well, and some tracts or nerves may be entirely or mostly unmyelinated. Thus, white matter is a generic term for concentrations of nerve fibers, myelinated and/or unmyelinated.

In contrast, gray matter is characterized by the presence of huge numbers of neuron cell bodies that are not distributed uniformly. Instead, they are aggregated into more or less identifiable sets referred to as gray matter *regions* in the vertebrate central nervous system or *ganglia* in the invertebrate nervous system. Alternately, they are sometimes referred to generically as *cell groups*—which are the origin of, or the termination site of, the various white matter tracts and/or nerves. In an oversimplified way, tracts are analogous to the highway system on a map, whereas regions are analogous to the cities and towns where the highways begin, end, or pass through.

When various specialized stains are applied to thin sections of central nervous system tissue (Appendix C), the regions become obvious (Fig. **6.4** right). It must be admitted, however, that it is easy to see a border around some of them, and not so easy (or even impossible) to see a border around others, which seem to merge imperceptibly into one another. One important reason that regions can even be distinguished is that there are many different neuron types (Chapter 2), which can vary in size, shape, staining intensity, and packing density. Fortunately, *particular sets of neuron types tend to cluster in recognizable gray matter regions (cell groups).* Because of this, *different regions have different functions*, and *a catalog of major regions amounts to a “parts list” of the nodes or centers of the circuitry that forms the central nervous system* (Appendix B).

The only reason regions can be recognized at all is that they show some pattern of cell staining that distinguishes them from other regions. However, the structure of regions is more complicated than this: it is the rule rather than the exception that *regions are formed by more than one interdigitated neuron type.* Furthermore, it is not uncommon that the interdigitated *neuron types are distributed in complex gradients* that are particular for each neuron type. As a matter of fact, each region in the central nervous system probably has a unique neuronal architecture that cannot be determined in anything other than an empirical way. This particular aspect of neuroanatomy is referred to as *cytoarchitecture*—or more generally *cellular architecture*.

For convenience, gray matter regions are often divided into two broad categories: *laminated* and *nonlaminated*. As the name implies, laminated regions display *layers*, and if they lie on the surface of the brain, they are often referred to as *cortex*—although by tradition, “cortex” has been reserved for laminated surface regions of the cerebrum (endbrain) and cerebellum. In contrast, nonlaminated cell groups are usually referred to as *nuclei* (the term was first used in this way by the neuroanatomist Christian Ludwig in 1779; the botanist Robert Brown named the cell nucleus in 1833), although nonlaminated cell groups with relatively indistinct borders are often referred to as *areas* or *regions* instead of nuclei. For clarity and consistency, there is now a strong preference to restrict in vertebrates the use of the term *ganglion* to gray matter regions in the peripheral nervous system. The problem is that historically, any distinct group of neurons in the central or peripheral nervous system was referred to by some researchers as a ganglion, and this usage has lingered in some current versions of neuroanatomical nomenclature. For example, the nonlaminated mass of the endbrain (cerebrum) is referred to as the “basal ganglia” in some textbooks, and as the “basal nuclei” or “cerebral nuclei” in others.

There is no fundamental reason why one gray matter region is laminated and another is nonlaminated. As a matter of fact, a homologous region may be laminated in one species and nonlaminated in another. For example, the dorsal part of the lateral geniculate complex, which relays sensory information from retina to primary visual area in the cerebral cortex, is distinctly laminated in cats, monkeys, and people but not in mice and rats (Fig. **6.5**). The primary taste relay cell group in the medulla, the nucleus of the solitary tract, presents an especially curious and dramatic case. In most fish, as in most other vertebrates, it is a nonlaminated cell group along the dorsomedial surface of the medulla, near the beginning of the spinal cord. However, in certain fish, the “nucleus” of the solitary tract forms a huge laminated lobe on either side of the brainstem. In these fish, taste buds have spread from the mouth and tongue to cover the surface of the fish's body, in a huge “gustatory map” that seems to be reflected in the structure of its

sensory relay cell group in the medulla. Without going into details, it would appear that the architecture of a gray matter region (as well as the shape of individual neurons) is dramatically influenced by the organization of its neural inputs, which is established during embryogenesis.

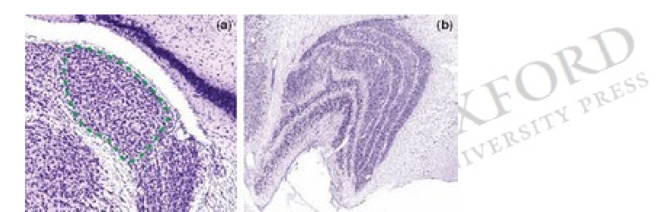




Figure 6.5
Cellular appearance of the same (homologous) gray matter region (dorsal part of lateral geniculate complex) in two different mammals. (*a*) In mice (here *Mus musculus*, C57-C1e), the dorsal lateral geniculate (surrounded by green dashed line) has a nonlaminated appearance. (*b*) In monkeys (here *Macaca mulatta*), the dorsal lateral geniculate displays an elegant laminated appearance. Screenshots of transverse Nissl-stained sections from http://www.brainmaps.org.

For the sake of completeness, we should mention that white matter tracts can range from simple (homogeneous) to exceptionally complex (heterogeneous), and from well circumscribed to diffuse and indistinct. At one extreme, we could cite the axons from the trochlear nucleus in the pons. The trochlear nucleus contains motor neurons that innervate just one of the tiny muscles that move the eyeball, and their axons course together through the roof of the pons in a very compact and homogeneous bundle or *central root*, cross the median plane, and leave the contralateral pons to form the trochlear *nerve*. The trochlear nerve central root is a very discrete, simple white matter tract in the brain. At the other extreme, the medial forebrain bundle—which stretches from one end of the brain to the other—has on the order of a hundred intermixed components, and it is diffusely organized with no clear borders anywhere. At the same time, it is exceptionally important functionally: in essence it is responsible for the expression of motivated and emotional behaviors.

Macroconnections, Mesoconnections, and Microconnections

In Chapter 3 we considered the organization of neural connections that form the neural network of invertebrates, and we have now seen the basic topographic organization of the vertebrate nervous system. This is a good time to review three basic approaches to describe, analyze experimentally, and model neural network organization in general.

At the very foundation of any neural network analysis is the concept of a *connection: the overall structure–function link between two nodes in the wiring diagram of the nervous system*. Building on this, *nodes* may be described at three successively greater levels of resolution and accuracy. First there are macronodes that correspond to gray matter regions, and they generate *macroconnections*. A macroconnection is a connection between two gray matter regions, and any given node can have multiple macroconnections associated with it; some are *inputs* from other nodes and some are *outputs* to other nodes. Second there are mesonodes that correspond to neuron types, and they generate *mesoconnections*. A mesoconnection is a connection between two neuron types, and again, any mesonode can have multiple inputs from other neuron types and multiple outputs to other neuron types. It is important to realize that macroconnection descriptions treat gray matter regions as black boxes, whereas the mesoconnection approach deconstructs a region into the individual contributions of each neuron type. And, third, there are micronodes that correspond to individual neurons, and they generate *microconnections*. Any micronode can have multiple microinputs and microoutputs. A synonym for connection is projection, whereas a *pathway* is that part of a connection demonstrated in a particular experiment or demonstration.

A diagram from Cajal summarizes the basic concepts associated with describing neural connections (Fig. **6.6**). At the macrolevel, two gray matter regions (retina and superior colliculus) are joined by a white matter tract (the optic nerve and its extensions to the superior colliculus). At the mesolevel, consider the retina—it consists of multiple neuron types arranged in three layers, and in each neuron type shown, information flows from dendrites and/or cell body to axon (arrows; the concept of functional polarity). Furthermore, only neuron type(s) in the inner layer (ganglion cells) send their axon through the optic nerve to connect with neuron type(s) in the superficial optic tectum. At the microlevel, each individual neuron would have at least a slightly different spatial distribution and functional activity that may be altered by experience.

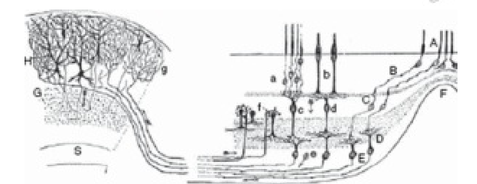


Figure 6.6
An illustration of two gray matter regions, their intrinsic neuron types and intraregional (local) connections, and interregional (extrinsic) connections from and/or to them. The retina (right) and superior colliculus (left) are shown, and the basic principles of structural organization and information flow (arrows) are discussed in the text. Key: A, cones in foveal (F) region; B, cone cell bodies; C, synapses between cones and foveal bipolar cells; D, contacts between bipolar and ganglion cells; E, ganglion cells; H, superior colliculus neurons; a, rod cell bodies; b, cone cell bodies in typical part of retina; c, rod bipolar cell; d, cone bipolar cell; e, ganglion cells; f, centrifugal axonal arborizations from visual centers that enter retina and encompass the cell bodies of amacrine cells; g, central axonal arborizations of retinal ganglion cells. From S.R. Cajal, *Textura del Sistema Nervioso del Hombre y de los Vertebrados: Estudios sobre el Plan Estructural y Composición Histológica de los Centros Nerviosos Adicionados de Consideraciones Fisiológicas Fundadas en los Neuvos Descubrimientos*, vol. 1 (Moya: Madrid, 1899, p. 84).

The qualitative structural distributions of macro-, meso-, and microconnections are genetically hardwired, but the quantitative features of microconnections can be greatly influenced by experience (see Chapter 12). The physical course taken by a connection through gray matter regions and white matter tracts is called its *route*, and route information is part of the description of a connection. Information about multiple connections can be arranged in a number of different ways involving more and more abstraction. For example, wiring diagrams include route information, connectomes are tables of connections, and basic plans include only high-level or minimally essential features.

A Nervous System Flatmap for Mammals

It seems obvious that a flatmap to display the organization of adult mammalian neural circuitry would be as useful as the flatmaps that have been developed over the centuries to display the surface of the earth for geography, transportation routes, and so on. One approach to the nervous system is based on the early embryonic fatemaps considered in Chapter 5 (Figs. 5.10–5.14)—starting with the neural plate that, of course, is topologically flat to begin with—and ending with the essential topographic divisions of the adult (Fig. **6.7**). We have learned that motor neurons tend to develop first, in the ventral or basal plate of the neural tube, ventral to the limiting sulcus (Fig. **6.2**)—after the primitive neural tube has differentiated into five secondary brain vesicles and spinal cord (Fig. 5.15 in Chapter 5). Here we have the basic topological principles of vertebrate central nervous system development: *transverse differentiation* into rostrocaudally arranged endbrain, interbrain, midbrain, hindbrain, afterbrain, and spinal cord; and *longitudinal*

differentiation into ventral (basal) and dorsal (alar) plates, at least in the spinal cord.

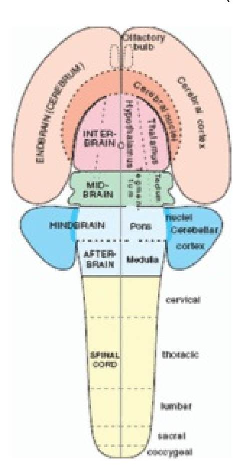








Figure 6.7
This flatmap shows the basic arrangement of the major topographic divisions of the adult central nervous system, scaled for the rat (see Figs. 5.10–5.14). There is broad acceptance of these divisions, leaving aside seemingly endless disputes about which synonyms to prefer. Adapted with permission from L.W. Swanson, The architecture of nervous systems, in: L.R. Squire, *Fundamental Neuroscience*, third edition (Academic Press: San Diego, 2008, p. 27).

In the rest of this section we will see how longitudinal differentiation of the neural tube proceeds in the brain, where it is not surprising that the process is not as simple as in the spinal cord and tends to become more enigmatic as the rostral pole is approached.

And now the brain: everyone seems to agree that the limiting sulcus of the early neural tube (Fig. 5.14 left in Chapter 5) can be traced uninterrupted from the caudal tip of the spinal cord all the way to the rostral end of the rhombicbrain, that is, to the junction between pons and midbrain (Fig. **6.7**). This is interesting in view of the observations of Benjamin Kingsbury (1872–1946) in the 1920s that the histologically defined floor plate of the vertebrate neural tube also stops at the pons/midbrain junction, and it suggests that alar and basal plates, which are so characteristic of the spinal cord, extend uninterrupted through the rhombicbrain.

In a way, the rhombicbrain is a rostral extension of the spinal cord that contains motor, sensory, and other neuron groups associated with cranial nerves rather than with spinal nerves. However, the rhombicbrain division of the neural tube has one major feature that distinguishes it absolutely from the spinal cord (and midbrain): a dorsal longitudinal zone known as the *rhombic lip*. This characteristic rhombicbrain specialization (Fig. **6.8**), whose presumptive earlier location is found along the lateral margin of the neural plate (Figs. 5.13 and 5.14 in Chapter 5), generates neural structures that clearly differentiate the rhombicbrain from the much simpler spinal cord. These structures include special sensory nuclei (for example, associated with hearing, balance, and the viscera), the cerebellum, and certain nuclei associated with the cerebellum (for example, the pontine gray and lateral reticular nucleus). It is almost as if the rhombic lip zone was added on top of the spinal cord architecture. As a matter of fact, it lies on top of the spinal cord extension into the rhombicbrain, the trigeminal complex (see Chapter 11).

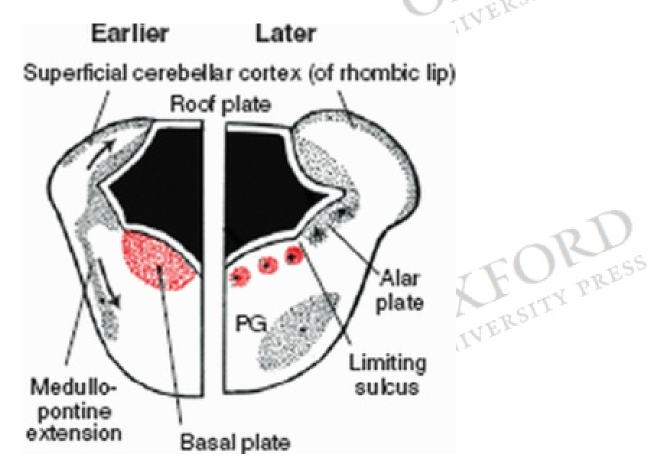




Figure 6.8
An early (left) and slightly later (right) stage of hindbrain development to show location of rhombic lip in transverse section (for location in neural tube see Fig. 5.14 in Chapter 5). The limiting sulcus on both sides divides the lateral walls of the neural tube into a thicker basal plate (red) and a thinner alar plate dorsal to the sulcus. The rhombic lip is separated from the alar plate by an obvious sulcus ventrally, and it continues dorsomedially as the roof plate, which of course is continuous across the median plane (separated here for clarity); the black octagonal area ventral to the roof plate is the fourth ventricle. Compare with the simpler pattern of spinal cord development (Fig. **6.2**). As hindbrain development progresses, specific gray matter regions associated with the cranial nerves differentiate by radial migrations of young neurons from the alar and basal plates. In stark contrast, many young neurons generated from the rhombic lip migrate tangentially (arrows on the left side) to form certain neuron types of the cerebellar cortex, as well as certain gray matter regions (like the pontine gray, PG) that project to the cerebellum. Adapted with permission from W.J. Hamilton and H.W. Mossman, *Human Embryology: Prenatal Development of Form and Function* (Cambridge: Heffer, 1972, p. 463).

According to most neuroembryologists who have examined the problem carefully, the limiting sulcus cannot be traced uninterrupted into the midbrain vesicle of the neural tube, and this is where uncertainty about the basic longitudinal organization of the central nervous system begins to creep in. What does seem to be true is that there are two longitudinal sulci or grooves running along the inner wall of the early midbrain vesicle. The more dorsal of the two grooves divides the vesicle into a dorsal “tectal” region and ventral “tegmental” region, whereas the more ventral sulcus divides the tegmental region into dorsal and ventral zones. The most important generalization about the midbrain is that sensory functions are usually ascribed to the tectum and motor functions are usually ascribed to the tegmentum. Unlike the rhombicbrain, but like the spinal cord, the developing midbrain vesicle does not have a stretched out roof plate (see Fig. **6.5** right).

Now we come to the primary forebrain vesicle, the most complex and uncertain of all. The first thing that happens after the endbrain and interbrain vesicles differentiate within it

is the appearance of two longitudinal grooves along the inner wall of the interbrain—the *hypothalamic sulcus* and *middle interbrain sulcus*. They are a consequence of the first neurogenesis in the region of the former primary forebrain vesicle, which takes place in the prospective region of a structure called the ventral thalamus, between the thalamus (dorsally) and hypothalamus (ventrally). Remember that in the spinal cord and rhombicbrain, there is a ventral to dorsal gradient of neurogenesis. In the interbrain (and midbrain), neurogenesis begins instead in an intermediate longitudinal strip (actually an arch that includes the ventral thalamus and retrochiasmatic region of the hypothalamus), then spreads to the bulk of the hypothalamus, and finally begins in the thalamus. And things get even more complicated: a third internal groove, the *habenular sulcus*, appears just ventral to the interbrain roof plate. The habenular sulcus divides the thalamus into epithalamus (most dorsal) and dorsal thalamus (between epithalamus and ventral thalamus). As a result, the interbrain vesicle can be divided into four roughly longitudinal strips, arranged from dorsal to ventral—*epithalamus*, *dorsal thalamus*, *ventral thalamus*, and *hypothalamus*. As a very broad generalization, the dorsal thalamus is basically sensory in function, whereas the rest of the interbrain (mostly ventral to the dorsal thalamus) is basically motor in function.

And finally, there is the endbrain vesicle (also known as the cerebral hemisphere or cerebrum) at the rostrodorsal end of the neural tube. The first sign of differentiation here is also the appearance of a roughly longitudinal, internal groove due to initial neurogenesis in the ventral half of the vesicle. This groove indicates division of the vesicle into its two basic parts, cerebral cortex dorsally and cerebral nuclei ventrally (where the neurogenesis begins). This *corticostriatal sulcus* appears at about the same time as the habenular sulcus in the interbrain, and it is followed shortly afterward by another longitudinal sulcus that further divides the cerebral nuclear region of the endbrain vesicle into a dorsal (striatal) ridge and a ventral (pallidal) ridge. In a very general way, it seems that neurogenesis in the endbrain vesicle progresses from pallidal ridge, to striatal ridge, to cortex. In the adult, it is common to regard the topologically dorsal cerebral cortex as having a “sensory” function, and the topologically ventral cerebral nuclei as having a “motor” function—although as we will see in the next chapter, it is more useful to regard the endbrain as a whole in terms of cognitive functions.

When we look at the embryonic central nervous system at a time when neurons are just beginning to be generated, we can see in each of the brain vesicles and spinal cord that these early neurons tend to come from ventral regions of the neuroepithelium and tend to have motor functions later on. This is clear in the rhombicbrain and spinal cord, where a continuous limiting sulcus divides the walls of the neural tube into basal (ventral) and alar plates. We can also see it in the midbrain, where the tectal sulcus divides the walls of the neural tube into tegmental (ventral) and tectal divisions; and in the interbrain, where the middle interbrain sulcus divides the walls of the neural tube into the ventral thalamic and hypothalamic divisions (ventral) and the rest of the thalamus. And finally, we can see it in the endbrain, where the corticostriatal sulcus divides the wall of the neural tube into cerebral nuclear (ventral) and cerebral cortical divisions. There is no way of knowing at this time whether the tectal, middle interbrain, and corticostriatal sulci are discontinuous, rostral components of an extended limiting sulcus, or whether they are completely independent features of the midbrain, interbrain, and endbrain vesicles.

In any event, this seems to be the basic transverse and longitudinal organization of the central nervous system. As embryonic differentiation continues, it is thought that each of the major divisions defined by the longitudinal and transverse grooves is further subdivided over and over into the final adult complement of gray matter regions, which of course are interconnected in very specific ways by a variety of white matter tracts. Exactly what the true regionalization plan or fatemap of the neural plate actually is remains to be determined, most probably by understanding the genetic program that builds the central nervous system over the course of development—an area of intense and exciting research.

In the mean time, at least four different schemes, based simply on interpretations of morphology, have been proposed. The original plan advanced by Wilhelm His in the late nineteenth century has already been described (Fig. 5.9a in Chapter 5), and it is shown schematically in Figure **6.9**. The key features of this interpretation are that *(a)* the presumptive floor plate extends to the rostral end of the neural plate, *(b)* at the earliest stages the rostral end of the neural plate is marked by the presumptive infundibulum—the stalk of the pituitary gland, and *(c)* the presumptive limiting sulcus, and thus the presumptive basal and alar plates, extend the length of the neural plate. The scheme outlined here is rather similar except that there is no presumptive floor plate (or a very different floor plate), presumptive limiting sulcus, or presumptive basal and alar plates in the midbrain and forebrain (**6.9**, Alvarez-Bolado/Swanson, right and left). Nevertheless, if the tectal, middle interbrain, and corticostriatal sulci turn out to be disconnected rostral extensions of the limiting sulcus, then the two models are remarkably similar. In the 1920s, Kingsbury proposed a third model where *(a)* the floor plate stops at the rhombicbrain–midbrain junction; *(b)* the basal plate extends across the midline rostral to the floor plate, and is thus continuous—with an inverted U-shape; *(c)* the alar plate also crosses the midline, rostral to the basal plate, so it too is continuous—with an inverted U-shape; and *(d)* the rostral end of the basal plate is found somewhere near the infundibulum. And finally, yet another scheme was proposed by the obscure yet brilliant Swedish neuroembryologists Bergquist and Källén in the 1950s. They suggested (Fig. **6.9**) that the prospective limiting sulcus, along with the prospective basal and alar plates, meet at the rostral tip of the neural plate.

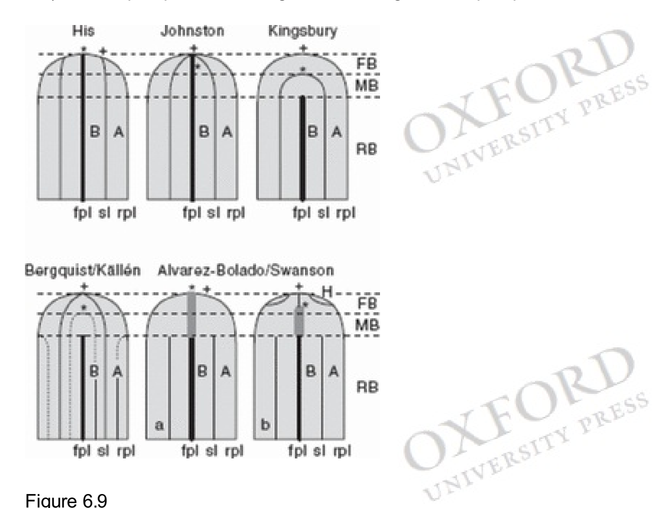




Figure 6.9
Different hypothetical schemes for basic regionalization in the brain division of the neural plate; see text for details. Key: A, alar plate; B, basal plate; FB, forebrain; fpl, floor plate; H, cerebral hemisphere (endbrain); MB, midbrain; RB, rhombicbrain; rpl, roof plate; sl, limiting sulcus. Adapted with permission from G. Alvarez-Bolado and L.W. Swanson, *Developmental Brain Maps: Structure of the Embryonic Rat Brain* (Elsevier: Amsterdam, 1996, p. 36).

Only time will tell whether any of these basic architectural plans is correct, or even whether this is a valid way of dissecting or parceling the central nervous system. But whatever the case may be, it is nevertheless valid to ask what relationship exists between the transverse and longitudinal parceling of the neural tube, and the organization of functional systems in the young, then mature, and finally aging brain. As argued in the rest of the book, the embryonic approach just outlined is like describing the body in terms of *topographic divisions* such as the head, neck, trunk, and limbs. In contrast, the functional approach is like describing the body in terms of traditional *systems*—nervous, digestive, circulatory, musculoskeletal, and so on. When we think of behavior, it is usually in terms of a particular act such as an arm with a hand (a topographic division) reaching for an object. The biological explanation of this behavior must be framed in terms of how all of the functional systems interact over both the short term and the long term. For example, the nervous system controls the musculoskeletal system of the arm and modulates the blood supply to this active tissue, and so on. Topographic divisions and functional systems are ways that biologists have come to describe how the body works; in a logic that I don't fully understand, they are complementary ways of dealing with the same object, the body.

To finish this section, let's return to the neural plate fatemap and simply point out the obvious: there is a continuous differentiation of gray matter regions (cell groups) and white matter tracts in the walls of the neural tube throughout the embryonic period of development. These various structures mature with strikingly different spatiotemporal patterns, and two of the larger units—the cortex of the cerebral and cerebellar hemispheres—differentiate incredibly massively and quite late (even partly after birth) in mammals. As a result, the areal proportions of regions shown on the schematic neural plate fatemap in Figure 5.14 of Chapter 5 (which is based on a very early stage of development) are useless for a flatmap of the adult central nervous system. One way to solve this problem is simply to make the area of a particular gray matter region in the adult flatmap proportional to its actual weight in the brain—while, of course, preserving boundary relationships between regions as much as possible. The results of this type of transformation for the adult rat central nervous system are shown in Figure **6.7**.

Overview: Parts of the Nervous System

If this chapter has seemed like a thinly veiled geography lesson, that is exactly what it is—the basic geography of the nervous system. It's like taking a globe and starting with an outline of the major oceans and continents (with their names), and then going on to show in more detail how the continents are divided into countries, the countries into states or provinces, and so on. It is true that from an historical perspective these boundaries and names are subject to change, but they nevertheless have two exceptionally important functions. First of all, they provide a vocabulary for describing locations on the surface of the earth. And second, they are used for constructing maps of the earth's surface that are complete, systematic, and geometric (topographic) inventories of geographic places or “parts.” As common experience teaches, maps are very handy and useful ways of transmitting geographic information, in a very abstract but at the same time accurate way. And as Gerardus Mercator made crystal clear in the sixteenth century, flatmaps are much handier for everyday use than globes.

The map we have outlined in this chapter illustrates the basic structural plan of the vertebrate central nervous system as based on what little is known about the development of the neural plate, the earliest and simplest representation of the central nervous system in the embryo. We can now go on in the next chapter to ask a fundamental question: what is the basic wiring diagram of the nervous system—how are the parts interconnected? This problem needs to be discussed in terms of the various topographic divisions, gray matter regions, and white matter tracts of the nervous system outlined here, as well as in terms of how individual neurons are interconnected to form specific networks, using the general concepts developed in Chapters 3 and 4.

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Oxford Medicine






Brain Architecture (2 ed.): Understanding the Basic Plan

Larry W. Swanson

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Brain and Behavior : A Four Systems Network Model

Chapter: Brain and Behavior
Author(s): Larry W. Swanson
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> *"Anyone who loves practice without theory is like a sailor going aboard ship without rudder or compass and having no idea where he is going."*
>
> Leonardo da Vinci
>
> *"Since Darwin and Poincaré, Einstein and de Broglie… scientific theories play a role in scientific progress that is just as essential as discoveries and the verification of experiments."*
>
> Jacques Roger (1997)

General theories about relationships between the nervous system and behavior have a long, and sometimes amusing, history that goes back well before the discovery of electrical impulses and neurotransmitters. Perhaps the first theory of any real merit was elaborated by Plato (c. 428–c. 340 BC) in his cosmology, *Timaeus*. He divided the mental and behavioral faculties (referred to then as the *soul*, and now as the mind) into three categories, each associated with a different level of the central nervous system and corresponding level of the body. The divine part concerned with intellect, reason, sensation, and voluntary movement was placed highest, in the brain, within the head. The mortal part dealing with the emotions came next, in upper regions of the spinal cord associated with the thorax, especially the heart. And the baser part subserving the appetites was lowest, in regions of the spinal cord associated with the abdomen and pelvis. Because it is desirable that these functions be partly shielded from one another, the neck forms an isthmus separating the intellect from the emotions, and the diaphragm separates the emotions from the appetites. Furthermore, this was a hierarchically organized functional model: the intellect influences the emotions, which in turn influence the appetites.

The next generation of theories was initiated about five centuries later by Galen (129–c. 217 AD), and it was not completely abandoned for an astonishing 1500 years or so. Initially, the theory rested on two pillars. First, there were the three interconnected ventricles of the brain, whose anatomy was described so thoroughly by Galen. And second, there was the hypothetical substance, activity, or force stored in the ventricles and responsible for nervous system functioning—Aristotle's *psychic pneuma* or animal spirits—the vehicle of the soul. By the tenth century these ideas evolved into a dynamic and generally accepted theory somewhat analogous to digestion, supplemented by the incorporation of Aristotle's basic psychological principles. The theory is beautifully illustrated in Figure **7.1**. It shows that all of the senses transmit images to the first ventricle (our right and left lateral ventricles, those of the cerebrum), which thus corresponds to Aristotle's *sensus communis* ("*common sense*")—the place where inputs from the individual senses are combined to produce holistic images and imagination. These images are then passed on to the second cell (our third ventricle), where they are manipulated by the process of reasoning; and finally, the residual is in turn sent to the third cell (our fourth ventricle), where it is stored as memory.

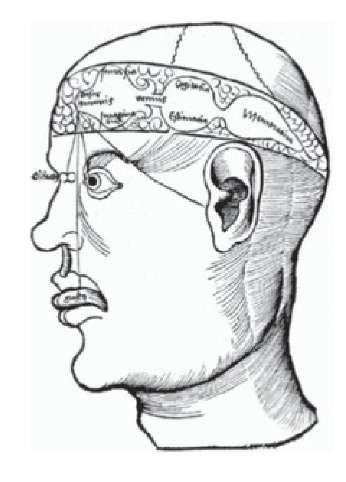





Figure 7.1

Vesalius (1543) mentioned that he used this particular ventricle man drawing in school to learn about the brain. It was published by Gregor Reisch in his *Margarita*

philosophica (1503), a collection of grammar, science, and philosophy that has been considered the first modern encyclopedia of any real merit. There is a horizontal "window" through the skull into the brain, showing three interconnected cavities surrounded by curly lines presumably indicating the cerebral convolutions. The rostral end of the rostral cavity or cell (our lateral ventricle) is labeled *sensus communis* (common sense), and this is where nerves for all of the special senses (indicated by lines from the sensory organs) converge. More caudally in the first ventricle one finds *fantasia* (fancy) and *imaginativa* (imagination). The passage between the first and second ventricles is labeled *vermis* (worm), and this refers to the choroid plexus "valve" that extends through the interventricular foramen (of Monro). The second ventricle (our third ventricle) Figure **7.1** (Continued) is labeled *cogitativa* (thought) and *estimativa* (judgment). The third cell or ventricle in this drawing corresponds to our fourth ventricle, and it is labeled *memorativa* (memory). The passage between the middle and caudal ventricle (which we refer to as the cerebral aqueduct of Sylvius) is unlabeled. For one of Vesalius's renderings of the brain, see Figure 10.10 in Chapter 10.

The last major addition to this theory was provided by René Descartes (1596–1650) toward the middle of the seventeenth century. He proposed that the flow of psychic pneuma up and down the hollow nerves was controlled by the soul, which he localized to a central position within the brain, in the tiny, unpaired pineal gland (Fig. **7.2**). As you can see, the Galenic model was essentially based on hydraulic principles learned from irrigation and plumbing—processing and regulating the flow of psychic pneuma through nerves, instead of water through ditches and pipes. As time went on, psychic pneuma was replaced with "nerve juice or fluid," then with animal electricity, and now with a combination of electrical impulses and neurotransmitter molecules. And analogies with hydraulic systems and clocks were replaced with analogies to machines, then telephone switchboards, and now with computers! Over the centuries, there has been an obvious tendency to describe brain function in terms of the dominant technology of the times.

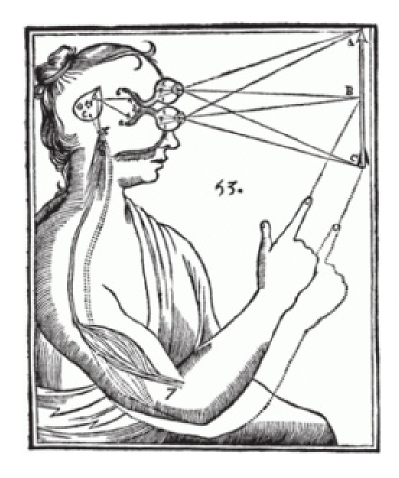




Figure 7.2
The first diagrams illustrating the principle of reflexes were published by René Descartes in his *L'Homme* (*Treatise of Man*). This illustration is from the 1664 edition in French, which was the language it was written in, and the edition containing illustrations supervised by Descartes himself. The earliest edition was published in 1662 in an unauthorized Latin translation, with very different figures.

Not everyone bought into the Galenic model. Most notably, the first great life scientist of the Renaissance (other than Leonardo), Andreas Vesalius (1514–1564), stated in his revolution-sparking masterpiece, the *Fabric of the Human Body* (1543), that the ventricular theory was unsubstantiated and unlikely, and that nerves did not look hollow to him. In fact, he even referred scornfully to the very drawing reproduced in Figure **7.1**. On the other hand, he was unable to offer any alternate explanations, theories, or models. The start of the third generation of general theories was left to Thomas Willis (1621–1675), who published the first book devoted entirely to the nervous system, the *Cerebri Anatomie*, in 1664. Here, Willis transferred the functions relegated during medieval times to the ventricles back into the brain substance itself—speculating that psychic pneuma is *generated* by gray matter and *transmitted* by white matter. He also speculated that the cerebral nuclei (which he discovered and named corpus striatum) receive all of the various sensory modalities and thus correspond to the "sensus communis," that the corpus callosum generates imagination, that the cerebral cortex is the seat of memory, and that together they control voluntary behavior. In contrast, he proposed that involuntary behavior and the vital functions of the body are controlled by the cerebellum.

As important as Willis's speculations were in shifting attention back to the brain substance itself, they were, after all, pure fantasy. The next real breakthrough was provided by the two great French experimentalists in the first half of the nineteenth century we have already met, François Magendie and Pierre Flourens. In 1822, Magendie demonstrated experimentally that sensory information enters the spinal cord through the dorsal roots, whereas motor commands to the muscles for behavior leave the spinal cord through the ventral roots.

In Magendie's nervous system, sensory information enters the spinal cord via one set of nerve fibers and its influence is reflected back out of the spinal cord through another set of nerve fibers to control the muscles (Fig. **7.3**). Without any inkling about underlying cellular mechanisms, Magendie demonstrated that there are *separate sensory and motor systems*, and that they have an *obligatory interaction within the central nervous system*. In the 1830s the pioneering British neurophysiologist Marshall Hall (1790–1857) named this arrangement the *reflex arc*. It is a fundamental part of all subsequent models of basic nervous system organization.

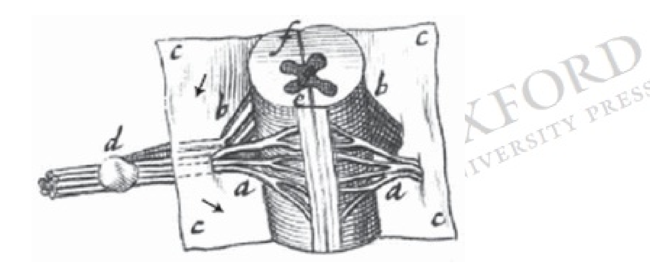




Figure 7.3
This illustration of Magendie's circle is from the first monograph on the spinal cord, by Gerard Blasius in 1666. In the *Anatome Medullae Spinalis et Nervorum inde Provenientium* he was the first to illustrate the dorsal and ventral spinal roots (as well as their rootlets), and the H-shape of the spinal cord gray matter, all of which were discovered by Volcher Coiter in 1572. Arrows showing direction of information flow were added. Key: a, dorsal root; b, ventral root; c, dura; d, spinal nerve ganglion, e, dorsal median sulcus; f, ventral median fissure. Photograph courtesy of the National Library of Medicine.

Flourens did for the brain what his teacher Magendie did for the spinal cord, and their results were presented almost simultaneously. Based on the first systematic experimental analysis of brain function (using experimental lesions), Flourens concluded that the cerebrum (endbrain) is the seat of sensation and intelligence, the cerebellum of motor function, and the rhombicbrain of vital functions. Flourens's stature was so great that by 1840 he was able to defeat Victor Hugo for a lone chair in the French Academy. As we shall see later, this authority was not necessarily good—based on his experimental results, Flourens strongly opposed the idea of functional localization in the cerebral cortex.

Despite the experimental results of Flourens, a recurring theme in the history we have been considering so far is functional localization in the nervous system. In fact, it would be hard to think of a better organizing principle for the history of neuroscience than the more and more accurate *localization* of different functions to distinct parts of the nervous system. However, the work of the experimentalists acquired a whole new interpretation when the full implications of the cell theory were finally applied to the organization of neural systems by a small though brilliant group of neuroscientists—with Cajal at the helm—toward the end of the nineteenth century. This was the neuron doctrine and its corollary, functional polarity, and the way they have been applied to simpler nervous systems was a theme of Chapter 3. It is now time to see how they apply to the basic organization of the vertebrate nervous system, and more specifically to the mammalian nervous system (including humans).

Reflex and Voluntary Control of Behavior

The first wiring diagrams of the nervous system based on the cell theory (the neuron doctrine) were published by Cajal in 1890, and in an important way they explained the results of both Magendie and Flourens (Fig. **7.4**). At the level of the spinal cord, the axon of a spinal nerve ganglion cell transmits sensory information into the spinal cord via the dorsal roots. This information goes directly, or is relayed by another neuron (an interneuron), to a motor neuron, whose axon leaves the spinal cord through a ventral root before innervating a muscle fiber. This describes the cellular architecture of the simplest reflex arc in terms of topographic divisions known long before Cajal's time.

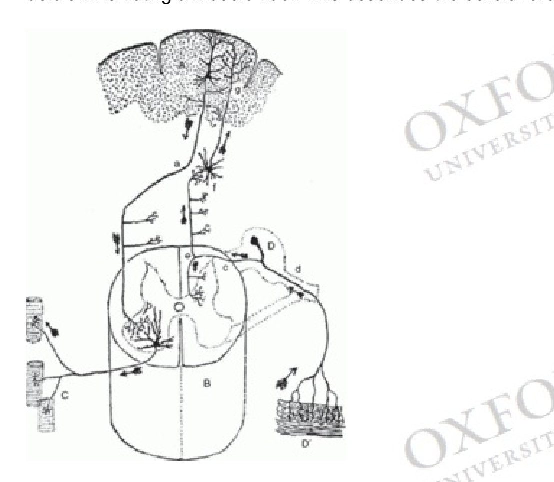




Figure 7.4
Cajal published in 1890 the first diagrams of reflex circuitry based on the neuron doctrine. In this diagram he showed how sensory information from the skin (D’) enters the spinal cord (B) by passing along the sensory fiber (dendrite; d) of a spinal nerve ganglion cell (D), and then its root fiber (axon; c) to the spinal cord (B). On entering the spinal cord, the axon bifurcates at (e). Some collaterals of bifurcation branches end in the spinal cord, and the rostrally directed bifurcation branch extends as far as the medulla (f), where it Figure **7.4** (Continued) ends on a neuron that eventually sends information to the cerebral cortex (g; Cajal was unaware of a relay through the thalamus for somatic sensory information). A second source of inputs to the spinal cord (a, b) arises from pyramidal neurons in the cerebral cortex (A). Sensory and cortical inputs to the spinal cord influence motor neurons that send an axon to striated motor fibers (C). Golgi method. From S.R. Cajal, *Les Nouvelles idées sur la structure du système nerveux chez l’homme et chez les vertebrés* (Reinwald: Paris, 1894, p. 25). See English translation by N. Swanson and L.W. Swanson, *New Ideas on the Structure of the Nervous System in Man and Vertebrates* (MIT Press: Cambridge, 1990).

However, Cajal made two other fundamental observations. First, he showed that “psychomotor” neurons in the cerebral cortex also send their axons to motor neurons in the spinal cord. So, motor neurons actually have at least two functionally different sources of axonal inputs or synapses: reflex inputs from sensory neurons and voluntary inputs from cerebral cortical neurons. His other fundamental observation was that in general, sensory information bifurcates in the central nervous system. Part of it goes to the motor system for initiating reflex responses, and part of it goes to the psychomotor or cognitive neurons for influencing voluntary responses. This organization is presented schematically in Figure **7.5**.

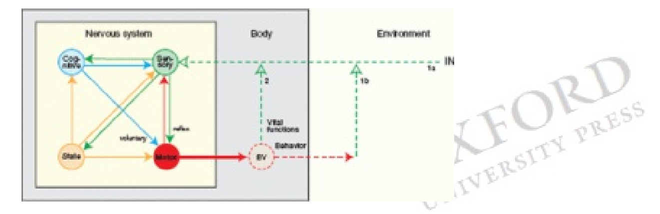


Figure 7.5
A four systems network model of the basic plan of the nervous system. One system—motor—controls behavior; in other words, behavior is a direct function of motor system output. The motor system is controlled in turn by three classes of inputs—from the sensory, behavioral state, and cognitive systems. Direct sensory inputs to the motor system mediate reflex behaviors (also see Figs. **7.3** and **7.4**), inputs from the cognitive system mediate voluntary behavior, and inputs from the third system mediate state control influences. The motor system influences the external environment via the skeletomotor system (B, behavior) as well as physiological responses within the body (V, vital functions). These influences on the external and internal environments provide sensory feedback signals to the nervous system (1 and 2, respectively; with 1a and 1b involving independent exteroceptive stimuli and feedback exteroceptive stimuli resulting from the animals behavior, respectively). Anatomical evidence suggests that the motor, sensory, behavioral state, and cognitive systems are strongly interconnected in the pattern indicated.

This is probably the most compelling and concise model of basic nervous system organization ever presented, and it is worth mulling over a little further before moving on. The first premise, which originally may have been implicit but now should be made explicit, is that *the motor system produces behavior*, or put another way, behavior is a function of the motor system. When we examine the behavior of another person or animal, we are observing the effects of the motor system via the motor nerves on the musculoskeletal system. The second premise is that there are *two major classes of functional inputs to the motor system: sensory or reflex, and cognitive or voluntary*; one originates in the

sensory nerves, and the other comes ultimately from the cerebral cortex. Presumably behavior may be controlled by either or both sources of inputs depending on circumstances. And the third premise is that sensory information bifurcates and goes to both the motor system and the cognitive system. Direct sensory inputs to the motor system produce involuntary reflex behaviors when they are strong enough, and inputs from the cerebral cortex mediate the voluntary initiation of the same behaviors. In either case, the same motor neurons control the behavior via their axons to the appropriate muscles.

The perceptive reader may have noticed that the sensory, motor, and psychomotor neurons in Cajal's circuit diagram (Fig. **7.4**) were replaced by terms with much broader meanings in the schematic representation of the diagram (Fig. **7.5**)—sensory system, motor system, and cognitive system, respectively. The justification for doing this is the topic of the next four chapters, but the short answer is that almost all parts of the nervous system can be thought of as parts of systems that control motor neurons, transmit sensory information, or form part of the cerebral hemispheres. But why "almost" all parts?

Behavioral State Control

In light of more recent evidence, there is a third class of inputs to the motor system that needs to be added to the basic wiring diagram proposed by Cajal—a system with intrinsic (spontaneous) neural activity that controls behavioral state (Fig. **7.5**). At the risk of stating the obvious, which we often tend to neglect, the activity patterns of most animals are related in a definite way to the day-night cycle, and in mammals this is governed by fairly regular periods of sleep and wakefulness. This is fundamentally important because the overall pattern of behaviors is very different during sleep and wakefulness. Put another way, the pattern of information flow to the motor system from the sensory and cognitive systems is fundamentally different during wakefulness and during sleep.

There is a neural system that is responsible for switching the overall function of central nervous system circuitry between two radically different states, sleep and wakefulness. And as a corollary of this, it is also responsible for orchestrating less radical differences between various stages of the sleep cycle (for example, deep and rapid eye movement stages), and various levels of arousal while awake. In essence, this system is responsible for controlling behavioral state, and its basic cyclicity is the result of an intrinsically driven clock or clocks, in principle just like there are intrinsic rhythm generators for breathing in the rhombicbrain and for the heartbeat within the heart itself.

Until recently, it was quite popular to analyze brain function only in terms of stimulus–response relationships. This approach, which was championed especially by a school of psychology known as behaviorism, liked to think of the brain as a passive machine, waiting for environmental stimuli to arrive and activate the appropriate response. What this approach chose to ignore was the fact that the brain is a *living* machine, and that it is operating all the time. At least three basic findings undermined the behaviorists. First, the brain actually uses just as much, if not more, oxygen when it is asleep as compared to when it is awake and "active." Second, there is a great deal of endogenously generated, intrinsic neural activity. And third, the motor system of embryos is quite active before sensory pathways have even developed to the point of establishing reflex inputs to it! We pointed out in Chapter 3 that most if not all neurons show some level of "spontaneous" activity, which is modulated up or down by synaptic inputs, and it is now clear that there are endogenous rhythm generators as well, some of which control behavioral state.

Feedback

Norbert Wiener (1894–1964) formally introduced *controllers*, *feedback*, and many other fundamental concepts about systems to biology in his revolutionary book, *Cybernetics*. It was published in 1948, just after the Second World War, and it played a major role in establishing the field known today as *computational neuroscience*, and one of its practical offshoots, *artificial intelligence*. We dealt briefly with the idea of behavioral state controllers in the last section, and now it is time to introduce the concept of *feedback* as it applies to the problem of the nervous system and behavior. Recall the basic plan developed in the last two sections (Fig. **7.5**)—behavior (motor system output) is modulated by three classes of input, from the *(a)* cognitive system, *(b)* behavioral state control system, and *(c)* sensory system. This provides systems or modules for the voluntary, reflex, and cyclical modulation of behavioral sequences. But what produces activity in these systems and how are their functions coordinated?

The sensory system is one direct source of input to the motor system, and we can close Magendie's circle of information flow by indicating that the results of behavior (Fig **7.5**, dashed arrow 1b), and information about vital functions within the body itself (like heart rate; Fig. **7.5**, dashed arrow 2), feed back into the sensory system. The central nervous system is thus constantly informed about what the animal has been doing—a record of its behavior—and what is occurring within the body itself, via feedback from the sensory system. Future behavior is influenced by past experience. We learn from our successes and failures; we try things again if they are positive experiences or we avoid doing things again if they are negative. Thus, we use feedback from behavior to remember what we have done, and to plan what we are going to do. And don't forget that sensory information is also transmitted to the cognitive and state control systems, and thus can alter their output as well.

What all of this implies is that in the awake state there is a constant flow of information from the sensory system to the motor, cognitive, and behavioral state control systems and that this flow is modulated by the consequences of behavior and changes in the body's vital functions. This mode of operation is much different in sleep, when the behavioral state controller inhibits the sensory and motor systems, leaving the cognitive system to dream.

This basic plan of nervous system organization is supported by a large body of well-documented anatomical, physiological, and chemical literature, which also shows unequivocally that the functions of all the systems are coordinated by an organized set of connections between them. We have already indicated that sensory information reaches each of the other three systems, and this is also true for the behavioral state system, which sends information (in the form of action potential patterns, and perhaps "hormonal" signals through the cerebrospinal fluid) to the other three systems. In contrast, the cognitive system tends to avoid directly influencing the behavioral state system, and the motor system appears to influence directly mostly the sensory system. In short, all four systems—motor, cognitive, state control, and sensory—are interconnected in a differentiated network that is modulated by sensory inputs from the body and external environment (Fig. **7.5**).

Topography versus Systems

The model of the nervous system we are discussing (Fig. **7.5**) is not structurally linear, say from rostral to caudal, and it is not hierarchical, say from higher levels to lower levels. Instead, it is distributed and interactive. Three interacting systems control the motor system and thus behavior, and they in turn are controlled interactively by extrinsic stimuli and intrinsic activity. We are dealing with a network not a hierarchy—or if you prefer, a distributed network not a hierarchical network.

This may seem like an overly simple, if not simplistic, basic plan for the nervous system, but it can be very useful for explanatory purposes if it accounts for known structure and function, and if it accommodates the results of future work. And notably, it bears no obvious relationship to the basic plan of the nervous system outlined in the previous chapter—a plan using the basic topographic divisions that differentiate within the walls of the neural tube. We now come face to face with two seemingly different fundamental plans of the nervous system, one based on *topographic divisions*—the endbrain, interbrain, midbrain, and so on—and another based on *functional systems*—motor, cognitive, state control, and sensory. As noted in the previous chapter, this is a classic dichotomy in anatomy: topography versus systems. Does one dissect and analyze divisions of the body such as the head, trunk, and limbs; or alternatively, does one dissect systems: circulatory, digestive, nervous, and so on? The answer is clear: both approaches are valuable—the hand is a topographic division with an obvious function, yet it also has components of many functional systems within it.

However, Figure **7.5** raises another issue: the use of highly schematic diagrams as opposed to the illustration of actual structure, or geometrically accurate anatomical relationships. The situation is exactly analogous to comparing the structural organization of the arteries, veins, and heart with Harvey's model of the circulatory system (Fig. **7.6**). One is physically accurate and the other is a simplified, logically correct diagram of functional significance (which Harvey confirmed experimentally). Again, both approaches are useful, valid, and complimentary.

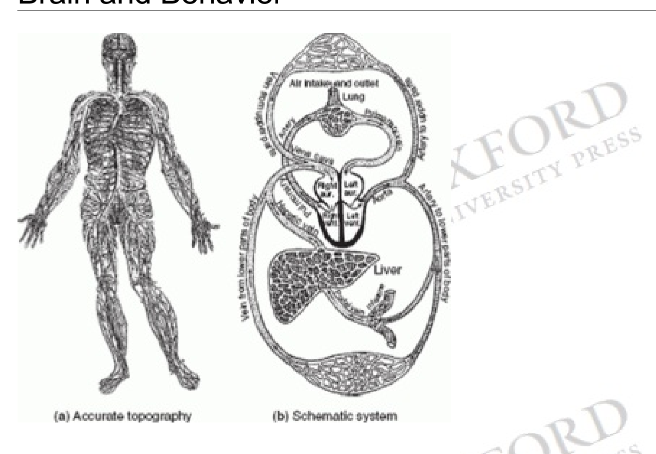


Figure 7.6
Alternate structural (*a*) and functional (*b*) ways of illustrating the circulatory system. The figure on the left shows the actual structural architecture of the human venous system and is from Andreas Vesalius's *De humani Corporis fabrica libri septem*, 1543. The figure on the right shows the entire cardiovascular system from a functional point of view—a double pump with a greater and a lesser circulation—based on the experimental work William Harvey published in 1628. It is from a drawing in C. Singer, *The Discovery of the Circulation of the Blood* (Bell: London, 1922, plate 1).

Nevertheless, when all is said and done, the relationship between the basic systems plan (Fig. **7.5**) and the basic topographic plan of the central nervous system (Fig. 6.7)—or even of the nervous system as a whole (Fig. **7.7**)—is not straightforward. This problem is actually the major focus of the next four chapters, on each of the major functional neural systems.

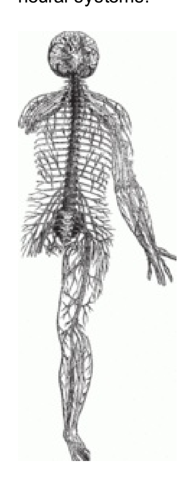


Figure 7.7
This view of the human nervous system as a whole is also from the *Fabrica* of Vesalius (1543). It shows the ventral aspect of the brain (that is, with the head tilted up), and the spinal cord remains within the vertebral column to strengthen the preparation. All other parts of the cadaver have been dissected away.

Overview: Defining Each System

Two and a half millennia after Aristotle began to formulate general theories about how the body produces behavior through the action of psychic pneuma, we can propose that the nervous system controls behavior via the motor system, which in turn is modulated by coordinated inputs from three systems: cognitive for voluntary control, sensory for reflex control, and intrinsic for behavioral state control. And at the cellular level, information flow through this network, which is modulated by feedback, is mediated by an alternating sequence of electrical and chemical events, along the axon and at synapses, respectively. But what is the relationship between these four functional systems and the basic topographic divisions that emerge as the nervous system develops in the embryo? The answer to this question depends on how the four systems are defined, and thus organized, and this is the topic of the next four chapters.

The strategy for defining the systems is time honored: deal first with the easiest systems to understand because their structural organization and functional dynamics are best understood, and then move to less and less characterized systems, and see what if anything is left unexplained at the end. The result suggests an interesting model: the nervous system as a whole is not a hierarchy like the army but instead is a network like the Internet, and each of its four subsystems has its own basic organization—the motor subsystem itself is hierarchical, the sensory subsystem is arranged in parallel, the cognitive subsystem is a network, and the behavioral state subsystem is like a sprinkler system.

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Larry W. Swanson

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The Motor System : Coordinating External and Internal Behaviors

Chapter: The Motor System
Author(s): Larry W. Swanson
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> *"The central organs form the connecting medium between all the nerves, or conductors of nervous influence. They act as exciters, or motors of nervous action, in determining the motor nerves to the production of contraction in muscles; and in this their action may be automatic, or voluntary…"*
>
> Johannes Müller (1843)
>
> *"We may distinguish two main groups of activities in the vertebrate organism which have determined the general plan of organization of the nervous system: actions in relation to the external world, and internal activities having to do with the processes of nutrition and reproduction."*
>
> J.B. Johnston (1906)

By definition the motor system is the output of the central nervous system. When I watch you eat a piece of candy, I am actually watching the immediate result of activity in your motor system, which, incidentally, is also controlling motor activity I can't directly see—your swallowing, gut peristalsis, sphincters, and heart beat. On the other hand, the sensory system provides input to the central nervous system, and the behavioral state and cognitive systems are intrinsic to it. We may summarize the basic wiring diagram or plan outlined in the previous chapter by saying that information processing in the central nervous system directs behavior via the motor system, which in turn is controlled by the behavioral state, cognitive, and sensory systems. This chapter is an introduction to the basic organization of the motor system, including its own subdivisions, and then the following three chapters go on to discuss in a similar way the three functional systems that control its output. As the quote at the beginning of the chapter from the pioneering American comparative neuroanatomist J.B. Johnston (1868–1939) alludes to, there is a long history of dividing bodily functions into two main categories: *somatic* and *visceral*. On one hand there is the "body" or soma with its musculoskeletal system and integument that together deal with the external world, and on the other hand there are all of the various internal, more or less automatic, visceral functions related to digestion, respiration, the circulatory system, and reproduction (see Fig 7.5, parts 1 and 2, in Chapter 7).

Motor Neuron Varieties

There are actually three different motor systems that are quite distinct from one another both in terms of structure and function (Fig. **8.1**). A good way to appreciate the differences is to begin by recalling the simple definition of a motor neuron in the nerve net of hydra (see Chapter 3, section on "Motor Neurons"). There a motor neuron is a neuron that sends its axon to a muscle cell, or more accurately, to a group of muscle cells (Fig. 3.6 in Chapter 3). For vertebrates, the best-known motor neurons are those lying in the ventral horn of the spinal cord and sending their axon directly to a group of skeletal muscle cells (Figs. 6.4 [in Chapter 6] and 7.4 [in Chapter 7]). They are part of the *somatic motor system* (Fig. **8.1** left) whose motor neurons control the muscles that move joints and certain other structures like the eyes—muscles that are typically attached to bone and under voluntary control but can be activated reflexively as well. They are also known as striated, somatic, or voluntary muscle cells, and while there may be subtle differences in the meaning of these terms, for our purposes they are essentially interchangeable.

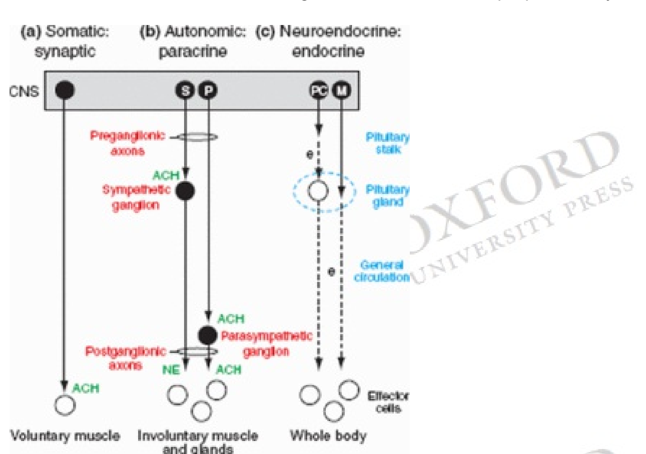




Figure 8.1
The basic arrangement of motor neurons (black circles) in the three major divisions (*a*–*c*) of the motor system. Key: ACH, acetylcholine; CNS, central nervous system; e, endocrine effect (dashed lines indicate transport of neurotransmitter through the blood); M, magnocellular system; NE, norepinephrine; p, paracrine effect; P, parasympathetic system; PC, parvicellular system; s, synaptic effect; S, sympathetic system.

The synapses formed by these *somatomotor* axons on striated muscle cells—synapses known as *neuromuscular junctions*—are the best understood of all synapses because they are so readily amenable to direct physiological analysis. They are highly differentiated both structurally and chemically, with a fairly rigid gap of about 20 to 30 nanometers (0.00002–0.00003 millimeters) between the pre- and postsynaptic membranes—the *synaptic cleft* that neurotransmitters (acetylcholine and others) diffuse across to influence muscle contractility. The acetylcholine receptors on the postsynaptic, muscle membrane are blocked by the South American arrowhead toxin, curare, and many of the classical "nerve gasses," and they are also attacked by autoantibodies in the disease myasthenia gravis. Obviously, paralysis is the result of blocking or inactivating acetylcholine receptors at the neuromuscular junction.

The second motor system, the *autonomic motor system*, is concerned with controlling the *viscera* and it differs markedly from the somatic motor system in two fundamental ways (Fig. **8.1** middle). First of all, there is a series of two motor neurons—one in the central nervous system and the other in a peripheral autonomic ganglion—that are referred to as the *preganglionic* and *ganglionic motor neurons* of the autonomic motor system, respectively. And second, there are two quite distinct divisions of the autonomic motor system, referred to as *sympathetic* and *parasympathetic*. Broadly speaking, the sympathetic system has short preganglionic and long postganglionic axons, uses norepinephrine as a major postganglionic neurotransmitter, and tends to act as a whole during stressful situations (during the "fight or flight" response to environmental threats). In contrast, the parasympathetic system tends to have long preganglionic and short postganglionic axons, uses acetylcholine as a major postganglionic neurotransmitter, and acts in a localized way that tends to antagonize the sympathetic system (it tends to have a restorative effect and to control digestion).

Most of the visceral organs, along with the blood vessels, receive a dual innervation by the autonomic motor system, with one division stimulating function and the other inhibiting function, in the process creating a dynamic balance. As a broad generalization, most autonomic motor system innervation is directed toward three cell types: smooth muscle, cardiac muscle, and gland. Just as *somatomotor neurons* were defined for the system that controls striated muscles, so various names have been applied to postganglionic neurons with specific functions. For example, autonomic *vasomotor neurons* innervate blood vessels and autonomic *secretomotor neurons* innervate gland cells.

At the level of the autonomic ganglia themselves, acetylcholine is the major neurotransmitter, and as at the neuromuscular junction, nicotinic acetylcholine receptors on the postganglionic membranes mediate the fast synaptic responses. It turns out that most if not all neurotransmitter receptors come in flavors or varieties, and this is true for neuromuscular and autonomic ganglion nicotinic receptors, although in both locations they are blocked by curare, and incidentally, stimulated by nicotine (hence the name). The fact that postganglionic parasympathetic neurons release acetylcholine onto visceral targets, whereas postganglionic sympathetic neurons release norepinephrine, has had vastly important implications for pharmacology—for the development of countless drugs that differentially influence visceral function in one way or another. Just as one example, heart rate is increased by sympathetic stimulation and is decreased by parasympathetic stimulation, or by drugs that interact with acetylcholine and norepinephrine receptors in the heart (agonists stimulate, and antagonists inhibit, the receptors).

Before moving on to the third motor system, one last feature of autonomic innervation should be noted. Very often, neurotransmitter is not released from a highly specialized synapse like the neuromuscular junction, where the very narrow synaptic cleft assures a "one to one" transfer of information from the presynaptic axon terminal to a specific region of the postsynaptic cell. Instead, autonomic neurotransmitters are often released in the vicinity of groups of cells with appropriate receptors, and the transmitters diffuse to interact wherever cognate receptors are found—hundreds to tens of thousands instead of tens of nanometers away. This arrangement—which is referred to as paracrine rather than strictly synaptic—is especially clear for the sympathetic innervation of blood vessels, which works like a lawn "sprinkler system," rather than a hose on a tree.

The third motor system, the *neuroendocrine motor system*, is centered in the hypothalamus and it controls the underlying pituitary gland. Here again there are two major divisions, this time referred to as magnocellular and parvicellular (Fig. **8.1** right). The *magnocellular division* consists of hypothalamic secretomotor neurons that send their axons to the posterior lobe of the pituitary gland, where they release neurotransmitters directly into the blood (the general circulation) to act as classical hormones on a variety of tissues and organs throughout the body. *Hormones* are molecules that are secreted into, and distributed throughout the body by, the blood to act on any tissues with corresponding receptors. Endocrinology deals with the glands that secrete hormones, as well as the effects of those hormones on target tissues. The *parvicellular division* of the neuroendocrine motor system consists of a separate set of hypothalamic secretomotor neurons that sends its axons to the hypothalamic end of the pituitary stalk. Here, in the median eminence, they release neurotransmitter hormones into a system of veins that delivers them to the anterior lobe of the pituitary gland. These parvicellular neurotransmitter/hormones in turn control the secretion of the all-important anterior pituitary hormones, which are synthesized by five classical cell types that will be discussed later.

Note that neuroendocrine secretomotor neurons exert their classical influence via the blood—in principle, they can influence every cell in the body that expresses an appropriate receptor, assuming of course that the concentration of neurotransmitter/hormone is high enough. The axon terminals of these neurons exert a hormonal influence, which is diametrically opposed to the incredibly focused influence of acetylcholine released by somatomotor neurons at the neuromuscular junction (acting strictly across a 0.02 micron gap on a patch of membrane with an area on the order of a few square microns).

Introduction to the Somatic Motor System: Flexion

This is the system that mediates the behavior we observe in other people: talking involves controlling the laryngeal muscles, reading involves moving the eyes in a highly patterned way, reaching involves controlling movements of the arm and hand, and so on. The basic mechanics of the system are familiar to everybody: the skeletal system of bones that is moved by the muscles attached to them. To take an example, extend one of your arms straight out, and then flex and extend it a couple of times. *Flexion* is accomplished by the biceps muscle, "on top" of the arm, whereas *extension* is accomplished by the triceps muscle, "on the bottom" of the arm. Together, they move the hand and forearm around a hinge called the elbow joint. The biceps and triceps are *antagonistic muscles* that flex or extend the forearm. Let's think a little more about how this arrangement works, how this behavior is mediated.

When your arm is at rest, there is actually tension in all of the muscles—in fact, under normal conditions when you are awake, all muscles are partly contracted; they have *tone*. This tone is actually controlled by a sensorimotor "proprioceptive" reflex (called a stretch or myotatic reflex) that helps set a "background" level of somatomotor neuron input to the muscle. The advantage of this situation is that now somatomotor neuron input to the muscle can be either increased or decreased: muscle tension can be either increased or decreased by inputs from the other three functional systems (behavioral state, cognitive, and sensory).

The biceps muscle is a *bundle* of many thousands of individual muscle cells that is innervated by a set or *group* of somatomotor neurons in a specific region of the spinal cord ventral horn. A *motor neuron pool* is defined as the set of neurons that innervates a particular muscle. Typically they only innervate one muscle (there is little or no divergence via axonal branching to more than one muscle). On the other hand, one motor neuron typically branches to innervate more than one muscle cell, called a fiber, within a particular muscle (see Fig. 7.4C in Chapter 7). Thus, as originally defined by Sherrington, a *motor unit* consists of a particular motor neuron and the set of muscle fibers that it innervates. In adult mammals, only one motor neuron is associated with each muscle fiber. This is basically how the nervous system controls one muscle—by regulating activity in a motor neuron pool dedicated only to that muscle. Left forearm flexion is caused by increased activity in the left biceps motor neuron pool of the spinal cord ventral horn.

Simple physiology experiments show that flexion is more interesting than you might think. When the biceps contracts, the triceps always relaxes at the same time, and vice

versa—when the triceps contracts the biceps relaxes. What this means is that when the biceps motor neuron pool is *stimulated* to produce flexion, the triceps motor neuron pool (consisting of different motor neurons) is *inhibited*, which of course results in less contraction (the triceps is relaxed). Similarly, when the triceps motor neuron pool is stimulated, the biceps motor neuron pool is inhibited. This arrangement maximizes the efficiency of movement during contraction because the antagonistic muscle is relaxed. The associated neural mechanism is called *reciprocal innervation* of antagonistic muscles across a joint.

The discussion thus far presents two basic features of how the motor system controls behavior—individual pools of motor neurons control individual muscles, and natural movements generally involve the coordinated activity of more than one motor neuron pool (and so, more than one muscle). Before considering how the coordinated activity of motor neuron pools is achieved, let's take a moment to think about the overall distribution of somatic motor neuron pools.

Distribution of Somatic Motor Neuron Pools

Our understanding of the motor system has a rock-solid foundation (one of the few in systems neuroscience): the overall distribution of motor neuron pools in the central nervous system. For the somatic motor system in particular, all of the pools are found in the spinal cord, rhombicbrain, and midbrain (Fig. **8.2**).

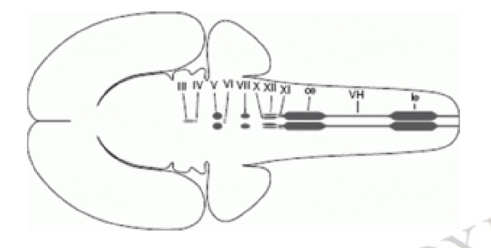


Figure 8.2
The distribution of somatic motor neuron pools illustrated on a flatmap of the rat central nervous system (see Fig. 6.7 in Chapter 6). Key: ce, cervical enlargement, III, oculomotor nucleus; IV, trochlear nucleus; le, lumbar enlargement; V, motor nucleus of the trigeminal nerve; VH, ventral horn; VI, abducens nucleus; VII, facial nucleus; X, nucleus ambiguus (of vagus nerve); XI, nucleus of the spinal accessory nerve; XII, hypoglossal nucleus.

There is a continuous longitudinal column of somatic motor neurons throughout the length of the spinal cord. These large, multipolar neurons are located in the ventral horn region of the spinal cord gray matter (Fig. 6.4 in Chapter 6), and motor neuron pools are arranged in such a way that those for flexor muscles tend to be dorsal to those for corresponding extensor muscles (Fig. **8.3**). In levels of the spinal cord related to the limbs (the cervical enlargement for the upper limbs, and the lumbar enlargement for the lower limbs), there is further organization. Motor neuron pools for muscles in the hand are lateral and dorsal, whereas pools for muscles progressively closer to the trunk tend to be progressively more medial and ventral.

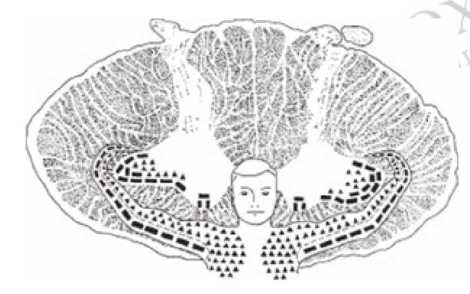


Figure 8.3
The general topographic distribution of somatic motor neuron pools as seen in a transverse section through lower cervical levels of the human spinal cord. Reproduced with permission from E.C. Crosby, T. Humphrey, and E.W. Lauer, *Correlative Anatomy of the Nervous System* (Macmillan: New York, 1962, p. 73). Reprinted with permission from Simon & Schuster.

It is curious that whereas there is a continuous distribution of ventral horn motor neurons down the length of the spinal cord, the axons of these motor neurons collect into distinct ventral roots (Fig. 7.3 in Chapter 7) before joining distinct *spinal nerves* (Fig. **8.4** and Chapter 11). The number of these spinal nerves varies in different species—for example, in humans there are typically 31 pairs and in rats 34. One has to wonder whether this regular arrangement of nerves reflects an underlying segmentation of the spinal cord, equivalent perhaps to the neuromeres that are so obvious in the brain during early embryogenesis (see Chapter 5, section on “Neural Tube: Transverse Brain Divisions”). Recent evidence shows that this is not the case. Instead, it is very clear that the bundling of motor neuron axons into discrete ventral rootlets and their aggregate roots is due to primary segmentation of the body wall itself. The axons grow into specific regions of embryonic body segments (specifically, the rostral halves of the somites; see Fig. 5.8 in Chapter 5), which are most familiar and easy to understand by remembering the regular arrangement of vertebrae, ribs, and their associated muscles and nerves in the thoracic (chest) region of the body (for the nerves, see Figs. 7.7 [in Chapter 7] and 8.4).

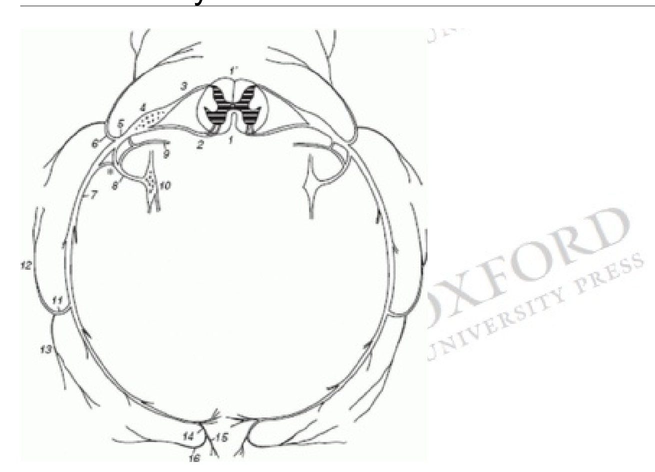




Figure 8.4
The arrangement of the human nervous system in one segment of the thoracic region. At this level the central nervous system is represented in transverse section by the spinal cord, and the peripheral nervous system is represented by the spinal nerves, spinal nerve ganglia, and sympathetic trunk ganglia. Compare with Figures 4.3, 6.4, 7.3, 7.4, 7.7, and **8.12**. Key: *1*, ventral median fissure; *1'*, dorsal median sulcus; *2*, ventral (motor) root; *3*, dorsal (sensory) root; *4*, spinal nerve ganglion; *5*, spinal nerve (common trunk); *6*, spinal nerve dorsal branch; *7*, ventral branch; *8*, communicating branch; *9*, meningeal branch; *10*, sympathetic trunk (paravertebral) ganglion; *11*, lateral cutaneous branch; *12*, dorsal limb of *11*; *13*, ventral limb of *11*; *14*, ventral cutaneous limb dividing into a medial limb *15* and a lateral limb *16*. From L.F. Barker, *The Nervous System and Its Constituent Neurones* (Appleton: New York, 1899, p. 323).

Somatic motor neuron pools in the brainstem send their axons into *cranial nerves* rather than spinal nerves, and this is not necessarily just a semantic distinction. The embryology of the head and neck is much more complex than that for the rest of the body, and, in the adult at least, there are anatomically separated motor neuron pools, or clusters of pools, for each cranial nerve that innervates striated muscle (Fig. **8.2**). With a little squeezing and fudging, neuroscientists have managed to fit all vertebrates into a 12 cranial nerve scheme, which was first outlined by Samuel Thomas von Soemmerring (1755–1830) in his medical school thesis of 1778. Which of them have components of the somatic motor system?

Starting with the most rostral somatic motor neuron pools in the adult and working caudally, there are three pairs of cranial nerves that are concerned exclusively with the six muscles that control the movement of each eye. The oculomotor nerve (cranial nerve III) innervates four of these extraocular muscles, and thus has four pools of motor neurons in the cell group (the oculomotor nucleus) that generates the nerve. In contrast, the trochlear (IV) and abducens (VI) nerves are very simple: each of them innervates a single extraocular muscle, and so the corresponding motor neuron pools in the brainstem (in the trochlear and abducens nuclei, respectively) contain only one motor neuron pool. The oculomotor and trochlear nuclei and nerves are within the midbrain, whereas the abducens nucleus and nerve are within the adjacent, rostral end of the pons. We will turn in the next section to the question of how activity in these three sets of nerves is coordinated to produce coordinated movements of the two eyes. This problem is similar in principle to mechanisms underlying the reciprocal innervation of antagonist muscles across a joint, referred to earlier in the chapter.

The muscles for chewing, and for moving the jaw in general, are innervated by the prominent motor nucleus of the trigeminal nerve (cranial nerve V), which lies in the pons and sends its axons through the motor root of the trigeminal nerve. The facial nucleus comes next. It lies in the caudal pons and/or rostral medulla and gives rise to the facial nerve (VII), which plays an exceptionally important role in nonverbal human communication—especially in the expression of emotional state. However, it is also very important in all mammals because, for example, it controls the muscles of the lips. When they are paralyzed, many animals cannot eat properly because food tends to drop out of the mouth. Think about your predicament after the dentist has anesthetized your "mouth"—including your lips! From an embryological point of view, the motor trigeminal (masticatory) nucleus innervates muscles associated with the first pharyngeal or branchial arch, and the facial nucleus innervates muscles associated with the second branchial arch (refer back to Figs. 5.2 and 5.4 in Chapter 5).

Next we come to a motor cell group with a curious name, the nucleus ambiguus (the "ambiguous nucleus" because it was difficult to identify in the early days). Structurally, it is unusual in as much as part of it contains pools of somatic motor neurons whose axons travel through two different cranial nerves. The most rostral pool innervates the stylopharyngeus, a tiny muscle that helps elevate the pharynx during swallowing and speech, and its axons travel through cranial nerve IX (the glossopharyngeal). However, the rest of the somatic motor neurons in the nucleus ambiguus send their axons into one of the most complex and important nerves of the body, the vagus nerve (cranial nerve X). The somatic motor neuron pools whose axons travel through the vagus nerve from the nucleus ambiguus innervate the larynx, and thus mediate speech in humans. In addition, they innervate the constrictor muscles of the pharynx, which are an integral part of the later stages of swallowing that are under reflex control. The somatic motor component of the glossopharyngeal nerve is associated with the third branchial arch, whereas the vagus nerve is associated with the remaining arches.

The last two, most caudal, somatic motor nuclei traditionally associated with cranial nerves are a bit confusing. One of them is the motor nucleus of the (spinal) accessory nerve (called cranial nerve XI). It has two motor neuron pools that are centered in the ventral horn of the first five or so cervical levels of the spinal cord, and the nerve that they generate innervates two muscles of the neck and shoulder region (the trapezius and sternocleidomastoid). In contrast, the hypoglossal nucleus clearly lies in the caudal region of the medulla, and it generates the motor nerve to the complex and fascinating musculature of the tongue (XII, the hypoglossal nerve).

Central Pattern Generators—Sets of Motor Neuron Pools

The last section, dealing with motor neuron pools, was a very straightforward description for the simple reason that the basic structure–function organization of these neuron groups, which generate the craniospinal motor nerves to the somatic musculature, is well established. Sherrington called them the "*final common pathway*" of the motor system because they integrate multiple inputs and are the direct output to behavior (Fig. **8.5**). In contrast, most of what we can say about the neuroanatomy of the hierarchically organized network that directly controls the patterned output of the final common pathway—the rest of the motor system—is fairly vague and hypothetical. And at this point the whole topic is associated with what can only be described as a chaotic terminology. Fortunately, there doesn't seem to be very much controversy about its general functional organization, leaving aside nomenclature.

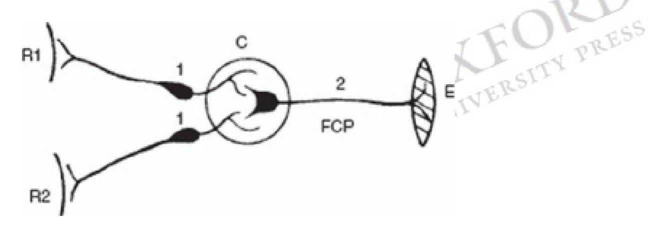




Figure 8.5
The concept of final common pathway (FCP) in the motor system. Key: C, neural center (gray matter region); E, effector; R1, R2: receptors 1 and 2; 1, inputs; 2, output. From C.J. Herrick, *An Introduction to Neurology* (Saunders: Philadelphia, 1915, p. 58).

What we do know is that the somatic motor system generates constantly changing patterns of activity that require more or less coordination between the hundreds of muscles on each side of the body. This has led to the concept of "*central pattern generators*," and a variety of related concepts such as central rhythm generators, and so on. As we shall now see, experimental evidence indicates that the motor system can be viewed essentially as a *hierarchical network of central pattern generators, initiators, and controllers*—with the final common pathway at the bottom of the hierarchy, just below the central pattern generators (Figs. **8.6** and **8.7**). Thus, the lowest level of the hierarchy is occupied by the motor neuron pools. Think of them as a piano keyboard—a motor neuron pool plays a note (more or less loudly), a specific set of motor neuron pools plays a chord (more or less accurately), and so on until in the end we have a symphony of behavior.

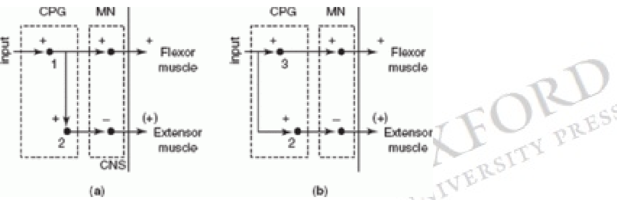


Figure 8.6
Two hypothetical models for circuitry underlying the reciprocal innervation of flexor and extensor muscles. The model in (*a*) involves two interconnected interneurons that form a simple central pattern generator (CPG). One interneuron is excitatory, +, and the other is inhibitory, –. The model in (*b*) involves two independent interneurons that are coordinated by a branched input. Key: CNS, central nervous system; MN, motor neuron; (+), less excitation.

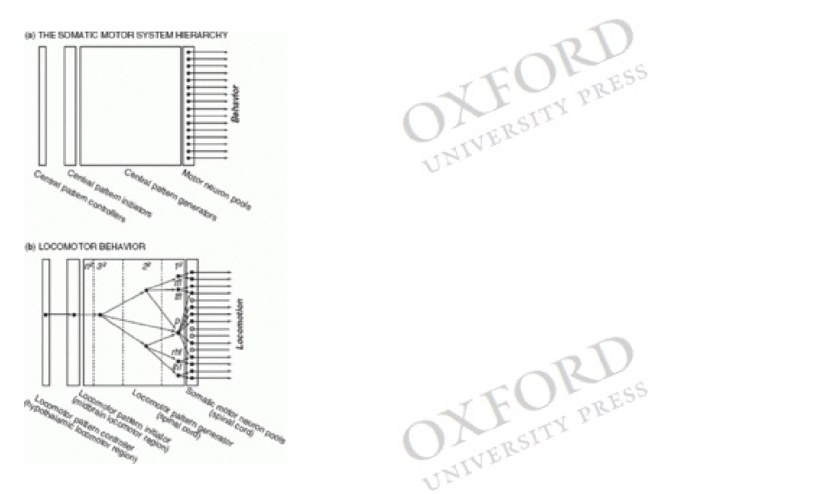




Figure 8.7
The core of the somatic motor system can be thought of as hierarchically organized, with motor neuron pools controlling behavior at the bottom (*a*). The basic organization of the neural system controlling a specific somatic motor behavior, locomotion, is shown in part (*b*). Note that there is a hierarchy of central pattern generators within the spinal cord locomotor pattern generator itself. Key: lfl, left forelimb motor neuron pools; lhl, left hindlimb motor neuron pools; p, postural motor neuron pools; rfl, right forelimb motor neuron pools; rhl, right hindlimb motor neuron pools.

Now let's return to the real-life situation we discussed in the last section, flexion and extension of the forearm across the elbow joint. Recall that when the biceps motor neuron pool (in the ventral horn of the spinal cord cervical enlargement) is excited, the arm flexes, and at the same time the triceps motor neuron pool (ventral to the biceps pool) is inhibited through a mechanism of reciprocal inhibition of the antagonist (triceps) muscle. Put another way, an excitatory neural input to the flexor motor neuron pool actually generates a patterned motor response that involves both the flexor and extensor muscles. The neural mechanism that generates this pattern is by definition a central pattern generator.

One simple model of the central pattern generator controlling reciprocal inhibition of antagonist muscles that is consistent with experimental evidence is shown in Figure **8.6**a. And we say "model" because it is not yet possible to examine histological sections of the spinal cord under the microscope and point with certainty to the precise neurons that form the simplest of central pattern generators. This is the frighteningly primitive level of understanding we are faced with in explaining the function of vertebrate neural systems. What we do know, however, is that to a first order of approximation, all mammalian somatic motor neurons are similar insofar as they excite muscle contraction by releasing the neurotransmitter acetylcholine. When a muscle relaxes, it is because there is less excitation, not because there is active inhibition of muscle fiber contraction via an inhibitory neurotransmitter. Thus, when the biceps contracts, the triceps relaxes because its motor neuron pool is inhibited by an inhibitory interneuron (2 in Fig. **8.6**a). This inhibitory interneuron is one part of the central pattern generator network for reciprocal innervation. The other part is an excitatory interneuron (1 in Fig. **8.6**a) that receives inputs (excitatory) and then relays them to the flexor motor neuron and to the inhibitory interneuron.

Figure **8.6**a is important and should be thoroughly understood because it is a simple example of how neural mechanisms are analyzed and described in terms of networks of excitatory and inhibitory connections. Information flows in one direction along the axons (away from the cell body and dendrites, which are indicated together by a filled circle for the sake of simplicity)—the principle of *functional polarity* discussed in Chapter 3, section on "Sensory Neurons." Another assumption in this model is that the same neurotransmitter (or mixture of neurotransmitters, really) is released from all the axon collaterals and synapses arising from a particular neuron. This is referred to as *Dale's principle*, which was named after Henry Dale (1875–1968), perhaps the greatest physiologist-pharmacologist of the twentieth century, who shared the Nobel Prize with Otto Loewi (1873–1961) in 1936 for their role in establishing the chemical nature of synaptic transmission. It is illustrated by interneuron 1, which excites both the flexor motor neuron and inhibitory interneuron 2 (thus inhibiting the extensor motor neuron and relaxing the extensor muscle).

Finally, one could look at this as a model of connections between four neurons, two in the central pattern generator and two different motor neurons. However, it is really a model of four neuron *populations*: the flexor and extensor motor neuron pools, and the corresponding groups of excitatory (1) and inhibitory (2) interneurons in the central pattern generator network that innervates the motor neuron pools. Thus, Figure **8.6**a is really an abstraction that shows the *elementary circuit* that explains the experimental data and

that can perform the task under consideration. The fact that the input in Figure **8.6**a ends on an excitatory interneuron and not directly on the flexor motor neuron (pool) is based on experimental results, not on any a priori assumptions.

An alternate model of how the central pattern generator network may be organized is shown in Figure **8.6**b. Here, there is also an excitatory interneuron (3) that innervates the flexor motor neuron (pool), and an inhibitory interneuron (2) that innervates the extensor motor neuron (pool). The difference is that in this second model the inhibitory interneuron is innervated directly by a branch of the input fiber to the excitatory interneuron—instead of by a branch of the excitatory interneuron (Fig. **8.6**a). Whether one or the other (or neither or both) model applies to a particular pair of antagonistic muscles needs to be determined experimentally.

Now we at least have models for the flexor central pattern generator involving the elbow—an excitatory and an inhibitory interneuron connected in stereotyped ways to two types of motor neuron (flexor and extensor). What is the next step in the analysis? We need to build a *hierarchy of central pattern generators*. Instead of voluntarily flexing your elbow, imagine holding out your arm with your eyes closed. If someone were to prick your hand with a pin, there would be an immediate withdrawal of the hand, and in fact, the whole arm would withdraw if the prick were strong enough. In neurological terms, each of the joints in the arm (and the shoulder) would flex in a certain order—a stereotyped sequence of flexor reflexes that are protective in nature—withdrawal reflexes.

As a matter of fact, there is a central pattern generator for regulating antagonistic muscles at each joint in the arm, but there is also a central pattern generator that regulates the sequence of flexion along the joints in the arm. In other words, we have a series of primary or first-order central pattern generators that in turn is regulated by a second-order central pattern generator. So the motor system hierarchy we have built so far includes the motor neuron pool layer at the bottom, then a layer of primary central pattern generators that innervate specific subsets of motor neuron pools (for example, related to the flexor and extensor muscles for a particular joint), and then a secondary central pattern generator that regulates the *sequence* of outputs from the primary central pattern generators. Of course the actual hierarchy for arm control is much more complex than this: just consider what is involved in controlling the hand alone, with five fingers, each with two or three joints themselves! But the principle remains the same; a hierarchy of central pattern generators coordinates the activity of the many muscles involved in any particular behavior.

We have just been discussing the possibility of a hierarchically organized network of central pattern generators involved in coordinating the movement of an arm—which has a whole series of joints from the fingers, through the wrist and then the elbow, to the shoulder. Now stop and think of an even more complex behavior: *walking*, which involves coordinating movements in all four limbs, along with movements across all the joints within each limb. This is obvious in four-legged animals, but it is also true in humans, where the arms swing alternately in a very stereotyped way (unless one is crawling!). Now let's return to the experimental and clinical data. We know that humans and animals with a completely severed spinal cord (where the spinal cord is completely disconnected from the brain) can still display coordinated *locomotor behavior* when the limbs are placed on a moving treadmill.

This remarkable fact indicates that there is a *locomotor pattern generator*, which is situated entirely within the spinal cord, and which can be activated by unconscious sensory information reaching it from nerves in the feet (and hands). We do not yet know the actual wiring diagram of the locomotor pattern generator network, but we do know that it exists, that it coordinates the incredibly complex sequence of muscle contractions involving *rhythmical movement* of all four limbs, and that it is an innate, genetically programmed, “hardwired” network that is fine tuned by experience. In a very general sense, it must be a hierarchically organized network of more localized pattern generators that control single joints, the series of joints along a particular limb, and finally the rhythmical sequence of limb activations characteristic of locomotion—including different stages of locomotion such as walking and running (Fig. **8.7**).

In essence, the locomotor pattern generator is a network of intraspinal interneurons that produces a complex behavior (pattern of muscle contractions) when activated by a combination of behavioral state, cognitive, sensory, and/or even higher order motor system inputs. Structurally, *the pattern generator is located near the set of motor neuron pools that it innervates*, so, for example, the locomotor pattern generator is entirely within the spinal cord. Before moving on to the highest levels of the motor system hierarchy (central pattern initiators and controllers), it is worth pausing for a moment to take an inventory of the major behavior pattern generators at the top of the central pattern generator hierarchy (Fig. **8.8**). Taking a broad view, they seem to fall into three rough groups.

Major behavior pattern generators	Central nervous system location
Breathing	Ventral medulla/upper cervical cord
Orofaciopharyngeal movements Facial expression Vocalization Licking, chewing, and swallowing	Parvicellular reticular nucleus (dorsolateral rhombicbrain)
Reaching, grasping, and manipulating	Cervical enlargement (spinal cord)
Orienting movements Eyes (oculomotor) Head and neck	 Dorsal midbrain tegmentum Cervical spinal cord
Posture	Spinal cord
Locomotion	Spinal cord

Figure 8.8
An overview of the major behavior pattern generators and their approximate locations within the mammalian central nervous system.

One group is obviously concerned with exploratory or foraging behavior. It includes the locomotor pattern generator in the spinal cord; pattern generators for orienting movements of the eyes, head, and neck; and of course supporting both of these there is a pattern generator for maintaining posture under the constant pull of gravity. Another group of behavior pattern generators appears to be more concerned with behavior after a goal has been approached. Reaching, grasping, manipulating, licking, chewing, and swallowing would be examples here. And finally, other pattern generators have a constant rhythmical activity as long as an animal is alive. A good example of this is the respiratory pattern generator in the ventral medulla and upper cervical spinal cord. Breathing is absolutely dependent on the intrinsic activity of this central pattern generator.

Central pattern generator networks that control the output of a particular set of motor neuron pools to generate a particular behavior are the neural substrate for what the ethologists refer to as *fixed action patterns—stereotyped behaviors elicited by specific stimuli* that can be more or less complex. There are many examples of a specific behavior (a fixed action pattern) that is released by a specific stimulus (called a sign stimulus). But one of the most interesting conclusions of the ethological analysis is that the central pattern generator that produces a fixed action pattern is itself activated by an innate releasing mechanism—a mechanism in the central nervous system that detects the appropriate stimulus and then releases the appropriate fixed action pattern. In other words, there is a *central pattern recognizer* that discharges when a specific pattern of stimuli is presented to an animal, and this discharge leads to the activation of a central pattern generator that in turn produces a fixed action pattern (behavioral response).

We shall now continue our analysis of the somatic motor system hierarchy by discussing the regulation of central pattern generators by innate releasing mechanisms or *central pattern initiators*.

Pattern Initiators and Controllers: Drive and Motivation

We have already mentioned that sensory reflex inputs from the ends of the limbs can activate the locomotor pattern generator. In addition, this generator can be activated by experimentally stimulating a part of the brain called the *midbrain locomotor region*—which lies deep to the inferior colliculus (the caudal tectum). That is, the locomotor pattern generator can be activated without somatic sensory reflex inputs from the spinal cord. The midbrain locomotor region is thus a *central pattern initiator*, and it in turn is controlled by regions of the forebrain that establish setpoints and other endogenous activity levels. For example, there is a *caudal hypothalamic locomotor region* (often referred to as the

subthalamic locomotor region) that appears to play a critical role in the spontaneous or intrinsic activation of the spinal locomotor pattern generator. The hypothalamic locomotor region is thus a *central pattern controller*, or part of a central pattern controller, at the top of the motor hierarchy for a particular behavior (Fig. **8.7**).

We think this is a valid model because animals without a forebrain do not show spontaneous locomotor behavior. On the other hand, essentially all of the forebrain except the caudal hypothalamus can be removed, and as long as the rest of the brainstem and spinal cord are intact, animals can display spontaneous, internally generated locomotor activity (Fig. **8.9**). This indicates that in some poorly understood way, a *hypothalamic locomotor controller* provides (either directly, or indirectly via the behavioral state system) a certain level of "*drive*" for locomotor behavior. However, the experimental evidence would also suggest that other parts of the hypothalamus, together with the cerebral hemispheres, mediate the actual *direction* and *planning* of that locomotor behavior, based on the selection of particular goals or goal objects—specific *motives* and/or *motivational states* if you will.

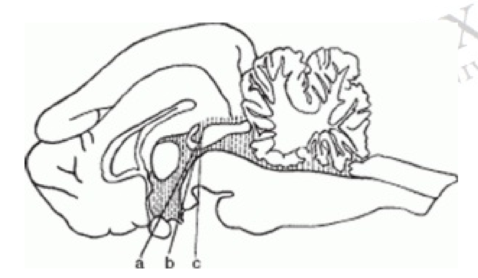


Figure 8.9
When the central nervous system is transected roughly between the midbrain and interbrain (line c), animals display no spontaneous locomotor behavior. They remain immobile until stimulated. On the other hand, animals with a transection roughly between interbrain and endbrain (or complete removal of the cerebral hemispheres, and the thalamus) display considerable spontaneous behavior. In fact, they can be hyperactive when the transection is at line b, but cannot spontaneously eat, mate, or defend themselves. Notably, these last three functions are preserved at a primitive level when the transection is just slightly more rostral, at line a. This evidence, combined with selective lesions or stimulation of the hypothalamus, suggests that the ventral half of the interbrain (hypothalamus) contains neural mechanisms regulating setpoints for locomotor and other classes of motivated behavior. Reproduced from J.C. Hinsey, S.W. Ranson, and R.F. McNattin, Role of hypothalamus and mesencephalon in locomotion. *Arch. Neurol. Psychiat*., 1930, vol. 23, p. 17.

And so we are faced with even more complexity. The highest level of the motor system hierarchy, that of central pattern controllers, is also hierarchically organized. For example, considerable experimental evidence indicates that the medial nuclei of the hypothalamus are critical nodes in controller networks for at least three specific classes of motivated behavior: ingestive (eating and drinking), defensive (fight or flight), and reproductive (sexual and parental). These *motivated behavior controllers* in turn must coordinate essentially all of the simpler behavior pattern generators listed in Figure **8.8**, for example, those associated with foraging behavior and the manipulation of appropriate goal objects.

And finally, we come to the hierarchy of motivated behaviors. This is a bit difficult to establish in mammals, where there is a great deal of flexibility in the sequence of behaviors. However, in the so-called lower vertebrates, and in the invertebrates, there is an incredibly sophisticated hierarchy of complex behaviors that are instinctive or genetically programmed, although to a lesser or greater extent they can be modified by experience. The most impressive and persuasive example was probably supplied by the Nobel Prize–winning ethologist, Nikolaas Tinbergen (1907–1988), who described in exquisite detail the sequence of behaviors (the ethogram) associated with the reproductive instinct in a special little fish, the three-spined stickleback (Fig. **8.10**). In males, the reproductive instinct consists of four sequential behaviors (fighting to establish a territory, building a nest, mating, and care of offspring), and each of these behaviors in turn consists of a specific sequence of less complex behaviors.



Figure 8.10
This rigidly organized hierarchy of behaviors associated with the reproductive instinct was described for the male three-spined stickleback fish by Nikolaas Tinbergen. If the behavioral sequence is interrupted at any point, none of following behaviors are expressed. Reproduced with permission from N. Tinbergen, *The Study of Instinct* (Oxford University Press: London, 1951, p. 104).

This example is very instructive in two ways. First, there is a true hierarchical organization because if the sequence of behaviors is interrupted in some way at any point, none of the "downstream" behaviors are expressed. And second, the entire repertoire of behaviors can be turned on or turned off, apparently by influencing the top of the hierarchy. Specifically, the display of the reproductive instinct as a whole is seasonal, and is only activated when the length of the day is within a certain range. This ensures that eggs are laid during the appropriate season (spring) for maximal survival, and it is undoubtedly mediated by the action of gonadal steroid hormones on brain networks during a certain time of the year (see Chapter 12, section on "Cycles").

It should be obvious by now that as we move up the motor system hierarchy, away from the motor neuron pools themselves, explanations become more and more vague, and the true situation in terms of neural networks also becomes more and more complex. Nevertheless, the basic pattern of motor neuron pools, central pattern generators, central pattern initiators, and then central pattern controllers described for locomotor behavior seems to be well established, and it probably applies to other complex behaviors as well.

Recent evidence suggests that there is a longitudinal column of distinct cell groups in medial regions of the hypothalamus and midbrain that controls the expression of motivated or goal-oriented behaviors, and the exploratory or foraging behaviors that go along with them (Fig. **8.11**). As mentioned earlier, the rostral segment of this behavior control column in the hypothalamus has controllers for the three basic classes of goal-oriented behaviors common to all animals, whereas the caudal segment has controllers for the exploratory behavior used to obtain any goal object. Rostrally, at least part of the control mechanism for ingestive behaviors (eating and drinking) is represented in the caudally directed (descending) division of the paraventricular nucleus; the control mechanism for reproductive behaviors includes the medial preoptic nucleus, ventrolateral

part of the ventromedial nucleus, and ventral premammillary nucleus; and the control mechanism for defensive (fight or flight) behavior includes the anterior hypothalamic nucleus, dorsomedial part of the ventromedial nucleus, and dorsal premammillary nucleus.

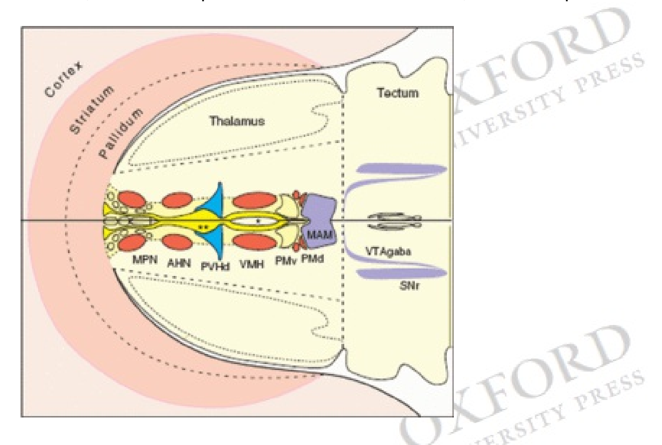


Figure 8.11
The basic organization of the hypothalamus and caudally adjacent regions of the midbrain on the flatmap. The dark yellow strip on either side of the midline represents the neuroendocrine motor zone (the rostral expanded tip indicates the GnRH region), with the pituitary stalk indicated by an asterisk and the neuroendocrine division of the paraventricular nucleus indicated by two asterisks. The light yellow region between the neuroendocrine motor zone and the medial nuclei (red, blue, violet) is the periventricular region, which contains a visceromotor pattern generator network and the suprachiasmatic nucleus (the master circadian clock in the brain). The medial nuclei and caudally continuous ventral tegmental area (GABAergic part; VTAgaba) and reticular part of the substantia nigra (also GABAergic; SNr) constitute the behavior control column discussed in the text; blue indicates ingestive behavior controller, red social behaviors (defensive and reproductive), and purple foraging behaviors. The hypothalamic lateral zone is lateral to the medial nuclei. Key: AHN, anterior hypothalamic nucleus; MAM, mammillary body; MPN, medial preoptic nucleus; PMd, dorsal premammillary nucleus; PMv, ventral premammillary nucleus; PVHd, caudally directed (descending) division of the paraventricular nucleus; VMH, ventromedial hypothalamic nucleus. Adapted with permission from L.W. Swanson, Anatomy of the soul as reflected in the cerebral hemispheres: neural circuits underlying voluntary control of basic motivated behaviors, *J. Comp. Neur.*, 2005, vol. 493, p. 126.

The caudal segment of the behavior control column begins with the mammillary body. At least the lateral mammillary nucleus is involved in signaling which direction the head is pointed (the function of the medial mammillary nucleus is not yet clear). The caudally adjacent reticular part of the substantia nigra is involved in controlling orienting movements of the eyes and head via projections to the superior colliculus. Finally we come to the ventral tegmental area, which appears to be involved in controlling locomotor behavior via mechanisms that remain to be clarified. Along with the nucleus accumbens it appears to regulate the amount of locomotor behavior, perhaps as a component of the "subthalamic (or hypothalamic) locomotor region."

The Autonomic Motor System

Our basic understanding of autonomic motor system organization was laid out through the brilliant work of two English neuroscientists, Walter Gaskell (1847–1914) and John Langley (1852–1925), toward the end of the nineteenth century. As already mentioned, the autonomic motor system—which has also been referred to as the *involuntary* or *visceral system* (in contrast to the voluntary or somatic system just reviewed)—is characterized by two sequential motor neurons (Fig. **8.1** middle). One motor neuron is in the central nervous system and is called preganglionic, whereas the other—the true final common pathway—is in a peripheral autonomic ganglion and so is called ganglionic (Fig. **8.12**). The general distribution of these motor neuron pools is illustrated in Figure **8.13**. Note that preganglionic sympathetic neurons are all found in and near a long, thin gray matter region referred to as the intermediolateral (or sometimes just lateral) column that extends down thoracic and upper lumbar levels of the spinal cord. The intermediolateral column is separate from, and dorsolateral to, the somatic motor neuron pools in the subjacent ventral horn (Figs. 6.4 [in Chapter 6] and 8.12). In contrast, preganglionic parasympathetic neurons—which typically mediate antagonistic effects to those of the sympathetic system (see section on "Motor Neuron Varieties")—are found in brainstem nuclei and in sacral levels of the spinal cord (in the intermediolateral column), rostral and caudal to the sympathetic column.

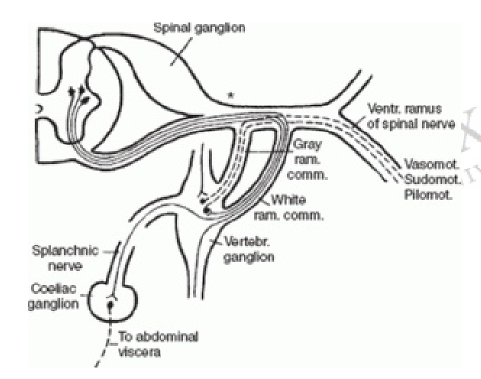




Figure 8.12
The basic arrangement of preganglionic and postganglionic axons in the sympathetic division of the autonomic motor system (see Fig. **8.1** middle). In the spinal cord, preganglionic axons arise from neurons in and near the intermediolateral column (a gray matter region), and then course through a ventral root to a paravertebral ganglion (Vertebr. ganglion; also see Fig. **8.4**), via a tiny offshoot of the mixed spinal nerve (indicated with an asterisk) referred to as a white communicating branch (ramus) because the axons are myelinated and thus have a whitish appearance. The postganglionic axons, which are shown as dashed lines, join the mixed spinal nerve through a separate gray communicating branch. Most of these axons are unmyelinated, hence the name. Some preganglionic axons extend through the paravertebral ganglia to join the splanchnic nerves and end in prevertebral ganglia (such as the celiac ganglion). Reproduced with permission from A. Brodal, *Neurological Anatomy in Relation to Clinical Medicine* (Oxford University Press: London, 1948, p. 347).

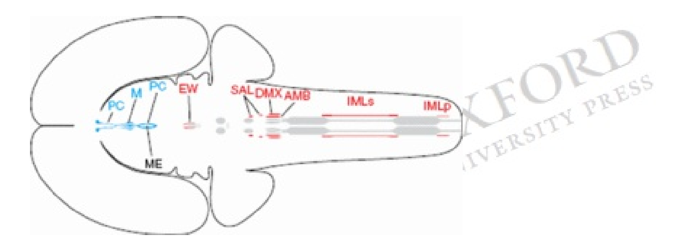




Figure 8.13
The distribution of visceral motor neuron pools (autonomic, red; neuroendocrine, blue) on a flatmap of the rat central nervous system. Motor neuron pools associated with the parasympathetic division of the autonomic system (P) include the Edinger-Westphal nucleus (EW), salivatory nuclei (SAL), dorsal motor nucleus of vagus nerve (DMX), nucleus ambiguus (AMB), and sacral intermediolateral column (IMLp). The sympathetic division is associated with the intermediolateral column in thoracolumbar levels of the spinal cord (IMLs). Motor neuron pools associated with the neuroendocrine system may be divided into magnocellular (M) and parvicellular (PC) divisions that are centered in the hypothalamus and surrounding the median eminence (ME) caudally (also see Figs. **8.11** and **8.14**). The somatic motor system motor neuron pools are shown in gray (see Fig. **8.2**).

Preganglionic autonomic motor neurons in the brainstem send their axons into several of the cranial nerves, where they course to parasympathetic ganglia in or near the organ that they innervate. Parasympathetic influences on the *eye* (control of pupil diameter and lens accommodation) are mediated by the oculomotor nerve (III), and the preganglionic axons come from a tiny cell group adjacent to the midbrain oculomotor nucleus, the Edinger-Westphal nucleus. *Salivation* and *crying* (tear secretion) are mediated by the salivatory nuclei in the medulla, whose axons travel through the intermediate (VII) and glossopharyngeal (IX) nerves. And finally, two medullary cell groups, the dorsal motor nucleus of the vagus nerve and part of the nucleus ambiguus, send preganglionic fibers through the vagus nerve (X) to parasympathetic ganglia innervating the *heart*, *stomach*, *small intestine*, and *upper colon*. Critical parasympathetic inputs to pelvic viscera, including the *bladder*, *lower colon*, and *genitalia*, are associated with preganglionic neurons in sacral levels of the spinal cord.

Sympathetic preganglionic neurons in thoracolumbar levels of the spinal cord send their axons to two classes of peripheral sympathetic ganglia. The first are called the paravertebral (or sympathetic trunk) ganglia for a very simple reason: they form a longitudinal chain of ganglia interconnected by bundles of axons that extends along either side of the vertebral column, a little like two strings of pearls (Fig. **8.12**), from the base of the skull to the coccyx. They are reminiscent of the ventral nerve cords in the more advanced invertebrates, and they are referred to as the *sympathetic trunks* with their *sympathetic trunk ganglia*. The second class of sympathetic ganglia lies much farther from the spinal cord, in irregular masses associated with visceral branches of the aorta (Fig. **8.12**) called prevertebral ganglia. They supply the abdominal and pelvic viscera, and the preganglionic fibers are carried by nerves referred to collectively as *splanchnic*. Most parts of the body are supplied with abundant postganglionic sympathetic nerve fibers (the central nervous system is a notable exception, except that it may have its own version in the guise of a remarkable noradrenergic cell group in the dorsal pons, the locus ceruleus or “blue spot”).

It is probably worth commenting on the striking fact that the autonomic motor system has a double output (pre- and postganglionic), whereas the somatic motor system has a single output (the somatic motor neurons). What if anything does this have to do with the fact that one system controls the viscera and the other voluntary muscle (the soma)? The simple answer is that whereas one particular somatic motor neuron sends its axon to one specific muscle, one preganglionic autonomic motor neuron can send axon collaterals to a number of different autonomic ganglia, and one postganglionic axon can branch to innervate a number of different organs or parts of organ systems. This is particularly true for the sympathetic division, which actually derives its name from ancient observations that responses in widely separate viscera throughout the body often can be surprisingly coordinated—they are “in sympathy.”

The dual, typically antagonistic, autonomic innervation of the body is highly organized, and there are stereotyped patterns of activity associated with specific behavioral states like exercise, fight or flight, hunger, and sleep. Probably the most famous and dramatic is the *emotional excitement* and *generalized sympathetic discharge* aroused in animals that are faced with extreme danger, like the sudden appearance of a predator. The famous Harvard physiologist Walter Cannon (1871–1945) studied this “*fight or flight response*” extensively in the 1920s. He showed that all of the coordinated sympathetic responses that accompany it are directed toward supplying as much energy to skeletal muscle as possible, sharpening the sensory modalities, increasing heart rate and blood flow—and decreasing functions that are not vital at the moment, like digestion. At the other end of the spectrum, during *sleep* the sympathetic division is relatively inactive, and the parasympathetic division comes into play, tending to restore energy supplies. As a general principle, Cannon showed that the opposing actions of the sympathetic and parasympathetic motor divisions play a critical role in maintaining *homeostasis*, or as Claude Bernard (1813–1878) had said in the nineteenth century, a relatively *constant internal milieu* for the body.

The obvious coordination of responses both within and between the two autonomic motor system divisions strongly implies that there is a hierarchical organization of *autonomic central pattern generators* for controlling responses in specific sets of preganglionic motor neuron pools, in a way quite analogous to that described for the somatic motor system (Fig. **8.7**). Unfortunately, however, we know very little about the organization, or even identity, of such autonomic pattern generators. One exception is a region of the *ventrolateral medulla*, close to the nucleus ambiguus and salivatory nuclei, that is involved in coordinating various aspects of cardiovascular homeostasis. Not surprisingly, central pattern generators for respiration are also found in this general vicinity (Fig. **8.8**).

The Neuroendocrine Motor System

As pointed out in the section “Motor Neuron Varieties,” the neuroendocrine motor system is the final common pathway for controlling the output of the pituitary gland—the master gland of the body's endocrine system. Its motor neurons are centered in the hypothalamus (Figs. **8.11** and **8.13**), and they fall into two classes, magnocellular, which are associated with the posterior lobe of the gland, and parvicellular, which are associated with the anterior lobe (Figs. **8.1** and **8.14**).

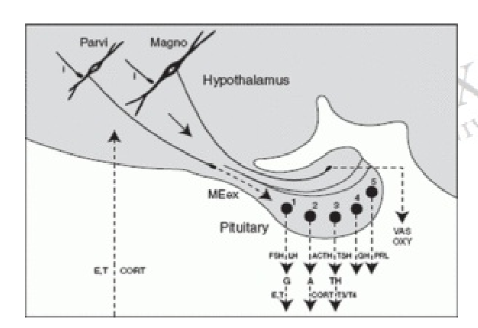




Figure 8.14
The two divisions of the neuroendocrine motor system in a schematic parasagittal view of the hypothalamus and pituitary gland of the rat. Axons of magnocellular

neuroendocrine neurons (Magno) end in the posterior lobe of the pituitary, where they release vasopressin (VAS) or oxytocin (OXY) into the general circulation as hormones. Axons of parvicellular neuroendocrine neurons (Parvi) end in the external lamina of the median eminence (MEex). Their neurotransmitters are released into hypophysial portal vessels that transport them as hormones to the anterior pituitary, where they exert endocrine effects on five classic cell types that in turn secrete hormones into the general circulation. Two sources of input to neuroendocrine neurons are shown: neural inputs (i) from other parts of the brain, and endocrine feedback inputs—for example, estrogen (E), testosterone (T), and corticosterone/cortisol (CORT). Key: A, adrenal cortex; ACTH, adrenocorticotropic hormone; FSH, follicle-stimulating hormone; G, gonads; GH, growth hormone; LH, luteinizing hormone; PRL, prolactin; TH, thyroid gland; TSH, thyroid-stimulating hormone; T3/T4, thyroid hormones.

The motor neurons of the *magnocellular neuroendocrine system* are found in the supraoptic and paraventricular nuclei (and scattered in between them), and they send their axons down into the stalk (infundibulum) of the pituitary gland to end in the posterior lobe, where they release hormones into the general circulation. There are two types of magnocellular neuroendocrine neuron. One of them normally secretes the peptide hormone *oxytocin* as its neurotransmitter, and this hormone plays a critical part in reproduction. First, it induces powerful contractions of the uterus during *parturition*, second it promotes milk release during *lactation*, and third it appears to promote positive *social behaviors*. The second type normally secretes the closely related peptide hormone vasopressin, which is also called antidiuretic hormone, and it plays an important role in controlling blood pressure and water balance. As the names imply, it is a powerful vasoconstrictor (by constricting small arteries it raises blood pressure), and it is a potent antidiuretic agent (by slowing the formation of urine it helps retain body water and thus increase blood pressure).

"Magnocellular" means "large celled" and this is an apt description. They are among the largest neurons in the brain and have an exceptionally high metabolic rate because they are synthesizing an exceptional amount of neurotransmitter. These neurons are also gland cells because they are secreting hormones into the blood, in high enough concentrations to reach and potentially influence all parts of the body. Oxytocin and vasopressin were the first of many neuropeptide neurotransmitters to be purified, characterized, and synthesized, an accomplishment that earned the Nobel Prize for Vincent du Vigneaud (1901–1978) in 1955.

The motor neurons of the small-celled or *parvicellular neuroendocrine system* that controls the anterior pituitary are found in and around the ventral wall of the third ventricle (Fig. **8.13**). It is hard to overstate the physiological importance of this system because of the hormones secreted by the five classical cell types of the anterior pituitary gland (Fig. **8.14**). One of these hormones (ACTH) controls the secretion of glucocorticoids (the steroid hormone cortisol, CORT, in humans) from the adrenal gland cortex. Blood levels of the basic metabolic fuel glucose are regulated by cortisol, which is secreted under all forms of stress. The stress response is critical for survival in the real world. Another hormone, thyroid-stimulating hormone (TSH), regulates the secretion of thyroid hormones, which control metabolic rate throughout the body. A third hormone, growth hormone (GH), is important for establishing body size during maturation, and then regulating metabolism in the adult. A fourth hormone, prolactin (PRL), stimulates milk production after childbirth, and the fifth and sixth are secreted by the final cell type, gonadotropes. They are perhaps the most important pituitary cell type of all because they control the secretion of sex steroid hormones (estrogen, E, and testosterone, T) from the gonads—and they in turn control the female cycle, sex drive in males and females, and even parental care. Without these functions the species would not survive.

So pituitary hormones control metabolism and body weight, body water and blood pressure, and gonadal and reproductive function. The pituitary is the master gland of the endocrine system, and its own output is controlled by pools of neuroendocrine motor neurons that are centered in the hypothalamus (Figs. **8.1**, **8.11**, and **8.13**). The neurovascular link between hypothalamus and anterior pituitary was hypothesized by Geoffrey Harris (1913–1971) in the 1940s. However, it took many years before Andrew Schally, Roger Guillemin, and Wylie Vale confirmed it by purifying and synthesizing the peptide neurotransmitter/neurohormones involved in signaling between hypothalamic nerve terminals and anterior pituitary cell types. They discovered after 25 years of intense research that hormone secretion from a particular cell type in the anterior pituitary is usually controlled by at least one stimulatory hormone and one inhibitory hormone from the hypothalamus (Fig. **8.15**). Later histochemical studies with specific antibodies showed that each hypothalamic neurotransmitter/hormone involved in controlling the anterior pituitary is synthesized by a different group of small neurons—the parvicellular neuroendocrine secretomotor neuron pools. Schally and Guillemin were awarded the Nobel Prize in 1977 for their work, after Harris had died and so was ineligible.

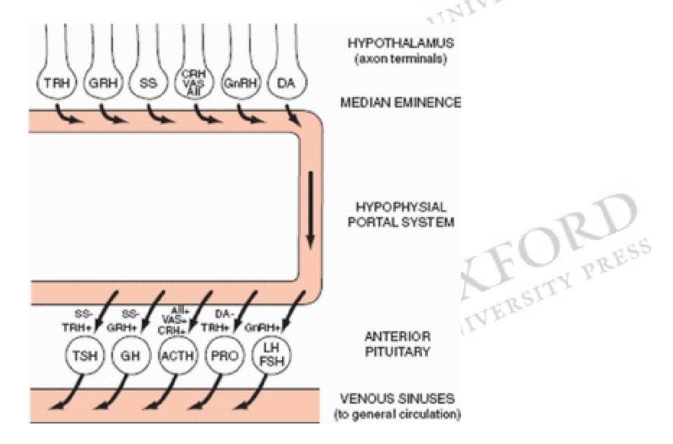




Figure 8.15
How neurotransmitter/hormones are secreted into the hypophysial portal system and transported to the anterior pituitary where they influence the secretion of hormones from the five classical cell types (see Fig. **8.14**). Key: ACTH, adrenocorticotropic hormone; AII, angiotensin II; CRH, corticotropin-releasing hormone; DA, dopamine; FSH, follicle-stimulating hormone; GH, growth hormone; GnRH, gonadotropin-releasing hormone; GRH, growth hormone–releasing hormone; LH, luteinizing hormone; PRO, prolactin; SS, somatostatin; TRH, thyrotropin-releasing hormone; TSH, thyroid-stimulating hormone; VAS, vasopressin. Adapted with permission from L.W. Swanson, The hypothalamus, in: A. Björklund, T. Hökfelt, and L.W. Swanson (eds.), *Handbook of Chemical Neuroanatomy*, vol. 5 (Elsevier: Amsterdam, 1987, p. 19).

Specific behavioral states are associated with activity in particular sets of somatomotor and autonomic motor neuron pools, and the same applies to the neuroendocrine motor system. For example, there are different, relatively stereotyped hormonal responses to environments that are too hot or too cold, to strenuous exercise, and to defending against a predator. Thus, one would suspect that there are neuroendocrine motor pattern generators, just as there are somatic motor and autonomic motor pattern generators. Actually, such a network has recently been characterized in the medial hypothalamus, in the periventricular region between the neuroendocrine motor neuron pools and the medial nuclei thought to be involved in the highest levels of the somatic motor control system (Fig. **8.11**; also see section on "Pattern Initiators and Controllers"). In addition, the baseline secretion of most pituitary hormones shows an underlying circadian rhythm (over a roughly 24-hour period) and ultradian rhythm (with a cycle time on the order of an hour or two). Neuroendocrine motor system output as a whole is thus mediated by central pattern generators and central rhythm generators—as is also the case for the somatic motor and autonomic motor systems.

The Cerebellum: Motor Coordination and Learning

In mammals, the cerebellum ("small brain," as compared with the cerebrum or "large brain;" so-named by Aristotle) is a very conspicuous mass (see the Frontispiece, and Fig. 6.7 in Chapter 6) that is attached to the brainstem by three pairs of thick white matter tracts, the cerebellar peduncles. As far back as 1664, Thomas Willis guessed that

the cerebellum is responsible for controlling what we would refer to as involuntary and autonomic motor responses, and almost 350 years later there is still no clear understanding of its function. The only thing that recent textbooks can seem to agree on (after admitting that it is not necessary for either perception or muscle contraction) is that somehow the cerebellum promotes the coordination and fine control of movement by influencing the output of brain motor and cognitive systems—although there are many interesting theories about how it may accomplish these functions.

In view of all this, it is hard not to consider the cerebellum as part of the motor system. But how does it fit into the scheme we have been developing in this chapter? Let's start with the elementary structure and wiring diagram of the cerebellum, and then go on to consider what its main inputs and outputs are in relation to the rest of the central nervous system. To begin with (Fig. **8.16**), the cerebellum has two basic parts, cortex and deep (basal) nuclei (like the cerebrum). Topologically, the cerebellar cortex is simply a sheet with three cellular layers (granule cell or deep, Purkinje cell or middle, and molecular or superficial layers). In many animals, including all mammals, the area of this sheet has been expanded greatly by a process of “corrugation,” which leads to innumerable folds or folia in the sheet. This cortical sheet forms the surface of the cerebellum, and as the name implies, the deep nuclei lie “underneath” the cortex, embedded in the white matter tracts that carry axons into and out of the cerebellum. This white matter has the quaint name *arbor vitae*, or tree of life (see the human brain in the Frontispiece).

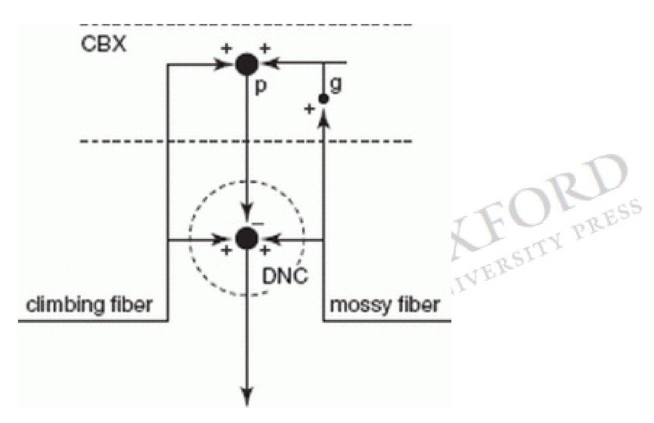




Figure 8.16
The elementary circuit of the cerebellum. For simplicity, interneurons of the cerebellar cortex are not shown. Key: CBX, cerebellar cortex; DNC, deep nuclei of cerebellum; g, granule cell; p, Purkinje cell; +, excitatory; –, inhibitory.

The elementary circuit of the cerebellum is quite interesting (Fig. **8.18**). First, there are two functionally and structurally distinct types of specific input to the cerebellum: mossy fibers and climbing fibers, both of which use excitatory neurotransmitters. Second, the output of the cerebellum is generated in the deep nuclei, which are excited by axon collaterals of both mossy fibers and climbing fibers. Therefore, in a sense, the simplest circuit involving the cerebellum consists of converging excitatory mossy and climbing fiber inputs to deep nucleus output neurons—which project to the motor system and to the cognitive system via the thalamus (see later discussion). Third, the climbing and mossy fibers go on also to provide excitatory inputs to the cerebellar cortex. And fourth, the cerebellar cortex in turn sends an inhibitory projection to the deep nuclei (via Purkinje cell axons). Thus, the flow of information through the excitatory climbing and mossy fiber collateral inputs to the deep nuclei can be modified by a delayed inhibitory feed-forward signal from the cortex.

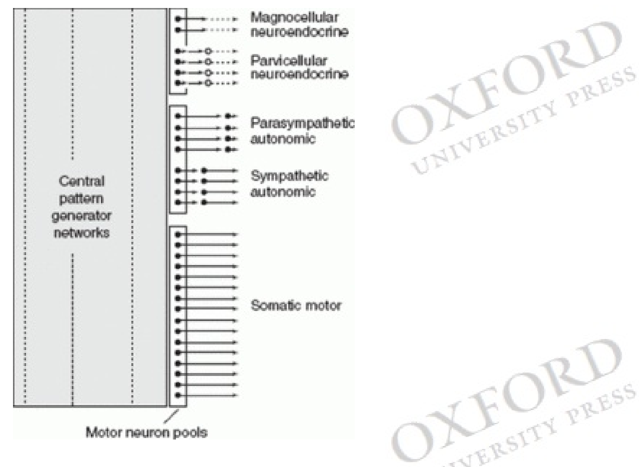




Figure 8.18
An overview of the three motor systems: somatic, autonomic (with sympathetic and parasympathetic divisions), and neuroendocrine (with magnocellular and parvicellular divisions). Presumably, central pattern generator networks that remain largely uncharacterized are involved in coordinating appropriate responses in all three systems.

The elementary cerebellar circuit illustrated in Figure **8.16** provides a beautiful model for considering the importance that *timing* can have on the function of neural networks. The basic idea here is that deep neurons and Purkinje neurons are in a position to *compare* activity in two classes of input, mossy fiber and climbing fiber. As the simplest possible example, it seems reasonable to expect that impulses arriving simultaneously at a deep neuron from a mossy fiber and a climbing fiber have an additive effect on the deep neuron, whereas unsynchronized inputs should have smaller effects. This type of thinking, combined with a more complete elementary model of the cerebellar cortex (that includes inhibitory interneurons), can lead to very fruitful exercises in mathematical modeling and experimental neurophysiological data gathering.

Much more intriguing, however, is the possibility (see Chapter 12) that synaptic strength can be increased or decreased by the coincidence detection of synapse activation: in other words, that *associative learning* can take place when two or more synapses act simultaneously. As a matter of fact, Richard F. Thompson and his colleagues have shown that the circuit illustrated in Figure **8.16** underlies at least some forms of *Pavlovian learning*, which is also referred to as *classical conditioning*. Recall Pavlov's hungry dogs and how they salivated at the sight of food (an unconditioned stimulus and response). What Pavlov did was to ring a bell just before food was shown to the dog, and the next time the bell was rung alone the dog salivated. Before the pairing, the bell alone did not elicit salivation, but after the pairing it did—it became a conditioned or learned stimulus that produced a conditioned or learned response. The key point was that an ineffective stimulus (the bell) became an effective stimulus after pairing with an unconditioned or already effective stimulus. We now know that the strength of a synapse associated with the auditory pathway was strengthened to the point where it was now

effective without pairing with the other stimulus. Where does this synaptic strengthening—this learning—take place?

Thompson's group has used a very simple model of Pavlovian learning. The unconditioned stimulus is a puff of air directed toward the eye (cornea), and the unconditioned response is a blink. For the conditioning stimulus a tone is played just before the air puff. Over a number of trials, there comes to be an eye blink at the time the tone is played, which actually protects the cornea from the air puff that is delivered a short time later. In a real sense, an anticipatory, protective reflex has been learned and it is associated with a previously neutral stimulus (the tone—like Pavlov's bell). Now here is the neurobiology (Fig. **8.16**). *Climbing fibers transmit the unconditioned stimulus* to the deep nuclei of the cerebellum and *mossy fibers transmit the conditioned stimulus* to the deep nuclei. Before training, the mossy fiber input stimulated by a tone is not strong enough to elicit a response in deep nuclei neurons, but after pairing with the unconditioned stimulus input to the deep nuclei the mossy fiber input becomes strengthened to the point where it can elicit a response. The basic memory of a very simple Pavlovian learned response is formed by changing synaptic strength in the deep cerebellar nuclei. From Figure **8.16** it is clear that the same information traveling through the mossy and climbing fibers also reaches the cerebellar cortex somewhat later. It is now known that this extra loop in the circuit helps refine and/or strengthen the basic response that is learned in the deep nuclei, especially as the time between conditioned stimulus and unconditioned stimulus increases.

The essential nature of cerebellar function remains elusive. However, it does appear safe to conclude that "the small brain" is an integral part of the motor system (it is also known to participate in visceromotor responses), and that it plays an important role in motor learning and in fine tuning the coordination between the hundreds of muscles involved in orienting responses, reaching and manipulating, posture, and so on. The cerebellum receives all types of sensory information, either directly from the spinal cord and brainstem or indirectly from the cerebral cortex (via mossy fibers from the pontine gray). After processing in the cerebellum, the resulting information is transmitted out through the cerebellar peduncles to central pattern generators and central pattern initiators in the brainstem and spinal cord (Fig. **8.16**), as well as to the cerebral hemispheres (the cognitive system) via a relay in the thalamus (see Chapter 10).

Overview: Integration within and between Motor Systems

It is hard to avoid concluding that the core of the motor system is organized in an essentially hierarchical way, with a large set of quite well-known motor neuron pools at the bottom level. On the other hand, the actual organization of the hierarchy in terms of neuroanatomically characterized networks remains only vaguely known. One way of summarizing the sketchy functional and structural evidence is illustrated diagrammatically in Figure **8.17**. The basic idea is this. First, a hierarchy of central pattern generator networks controls the system's output, the motor neuron pools. A primary central pattern generator innervates a specific set of motor neuron pools and thus produces a specific pattern of responses (say contractions in a specific set of muscles) and thus a specific behavior. A secondary central pattern generator network innervates a specific set of primary central pattern generators, thus producing a specific set of behaviors, and so on. Second, a central pattern initiator projects to the top of a central pattern generator hierarchy for a specific complex behavior (a good example is the spinal locomotor pattern generator, which is activated by a midbrain locomotor pattern initiator). Third, central pattern initiators appear to be under the control of central pattern controllers that are thought to impose setpoints and/or provide intrinsic "drive" or spontaneous activity levels for certain behaviors. And fourth, a great deal of motor coordination and motor learning appears to occur in the cerebellum, which projects to the central pattern generator and initiator levels of the hierarchy.

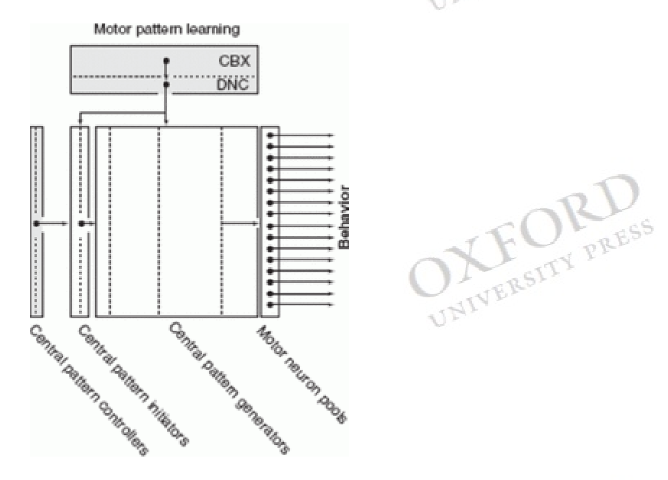




Figure 8.17
The core motor system is hierarchically organized, with the addition of the cerebellum that is involved in motor pattern coordination and learning (also see Figs. **8.7** and **8.16**).

In a way, it would appear that two quite different mechanisms control the output of the core motor neuron pool–central pattern generator–central pattern initiator hierarchy. On one hand, there are the central pattern controllers (which for motivated behavior lie in the hypothalamus), and on the other there is the motor learning network (a central pattern learner?) in the cerebellum. The cerebellum does not fit easily into a hierarchical model of motor system organization. Taken as a whole, the circuitry outlined in Figure **8.17** for the somatic motor system is organized as a network and not a strict hierarchy, because of the cerebellum and its input–output relationships.

As if this were not enough, it is essential that we recall one more wrinkle: there are three motor systems—somatic, autonomic, and neuroendocrine—and their activity is coordinated. In fact, as mentioned before in this chapter, various behavioral states are characterized by more or less stereotyped, coordinated responses in all three systems (Fig. **8.18**). Precisely how this coordination is accomplished in neural network terms remains to be clarified, but recent anatomical evidence does suggest that the medial hypothalamic central pattern controllers for motivated behavior also project to a medially adjacent visceromotor pattern generator network that coordinates both autonomic and neuroendocrine responses (Fig. **8.11**).

In the end, behavior is produced by a core motor system hierarchy that is organized along the lines illustrated in Figure **8.17**—including a cerebellar network that is critically involved in associative motor learning. The output of the motor system as a whole is controlled by three classes of input—from the cognitive, sensory, and behavioral state systems (Fig. 7.5 in Chapter 7).

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Oxford Medicine





Brain Architecture (2 ed.): Understanding the Basic Plan

Larry W. Swanson



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The Behavioral State System : Intrinsic Control of Sleep and Wakefulness

Chapter: The Behavioral State System
Author(s): Larry W. Swanson
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> *"The periodical recurrence of sleep and the waking state is, therefore, essentially connected with something in the nature of animals, and is not dependent on the simple alternation of day and night. But the periods of sleeping and waking, in accordance with a pre-established harmony of nature, have been made to agree with those of the earth's revolutions."*
>
> Johannes Müller (1843)

If you are like most people, you spend about a third of your time asleep, and while you may not have stopped to think about it, sleep and wakefulness are obviously two entirely different behavioral and mental states. When you are asleep, gentle sensory information doesn't seem to "get in" and your muscles are relaxed—essentially there is no overt behavior, except for breathing and rolling over now and then. No one has come up with a convincing explanation for why we sleep, but there must be one because it has such a long evolutionary history—alternating periods of sleep-like behavior and wakefulness are found in all vertebrates and have even been detected in many invertebrates like mollusks and insects.

When all is said and done, the sleep-wake cycle is the primary organizer of behavior. So long as you are asleep there is no overt behavior that one would call voluntary in everyday language. Thus, the sleep-wake cycle provides a starting point or framework for analyzing behavior (in other words, the output of the motor system) in a formal or systematic way. If we consider a typical 24-hour day (Fig. **9.1**), about a third of it is spent in an essentially continuous period of sleep, if we are lucky! Then we awake and begin to spend the day doing one thing after another until night comes and we eventually start another cycle by going to sleep again.

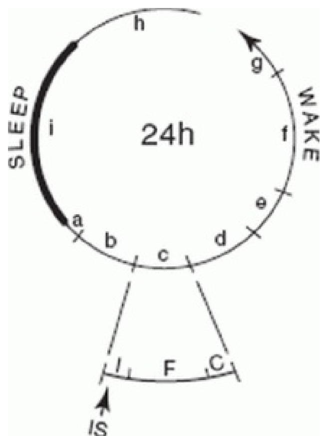






Figure 9.1
The sequence of behaviors (a through i) executed over the course of a typical day. Time is shown by the circle with an arrowhead. A complete behavioral episode carried out while awake (c) can be divided into three sequential phases: initiation (I), procurement or foraging (P), and consummatory (C), which includes a satiety mechanism for terminating the episode and a reward mechanism for influencing the probability that a similar episode will be repeated in the future. Key: IS, initiation stimulus.

From a scientific point of view, there are two important questions to ask and try to answer. First, what is the exact sequence of behaviors that are performed during the course of the day? We can simplify the problem by making the seemingly reasonable assumption that only one type of behavior can be performed at a time (a through i, Fig. **9.1**), although one *behavioral episode* could be very brief. And second, why is a particular behavioral episode performed at any particular time? In other words, how are alternatives prioritized, and why does switching between behavioral episodes take place? From the structural perspective we are pursuing in this book, we would like to know the organization of neural networks that mediate switches between behavioral states, changes in priorities, and altered levels of arousal. These problems go to the very heart of

nervous system function and only the first can be answered with any degree of certainty at the present time. We can begin to approach the second by dividing each behavioral state (sleep and wakefulness) into components, and then dividing those components into fragments that lend themselves to neural systems analysis.

If the primary level of behavior analysis involves characterizing alternating periods of sleep and wakefulness, the secondary level involves characterizing the sequence of behaviors during wakefulness, as well as the fascinating repeating sequence of *sleep stages* that are displayed by all mammals. These stages were defined on the basis of human EEG (electroencephalograph or "brain wave") recordings in 1953 by Eugene Aserinsky (1921–1998) and Nathaniel Kleitman (1895–1999), who scored a major conceptual breakthrough with this discovery. They showed that there is an alternation between what is called *rapid eye movement (REM) sleep*, when the cortical EEG is desynchronized (as in conscious attention) and vivid dreaming almost always occurs, and *deep sleep* (or non-REM sleep)—when dreaming is less vivid and perhaps less frequent. So there is an elaborate structure to the sleep state, and it is even more complex than first realized. Now we know based on characteristic patterns of the EEG that there is a sequence of four stages in a typical bout of deep sleep itself. In humans there is a startlingly regular cycle of alternating REM-deep sleep bouts during the course of an 8-hour period of sleep (Fig. **9.2**). In the average adult each bout of REM-deep sleep lasts about an hour to an hour and a half, although bout length tends to decrease from childhood, through adulthood, and on into old age.

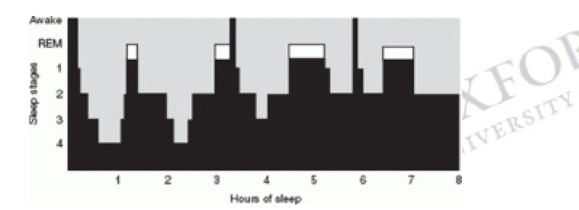


Figure 9.2
The stages of sleep for a typical adult human over an 8-hour period. Adapted from R.J. Berger, The sleep and dream cycle, in: A. Kales (ed.) *Sleep: Physiology and Pathology* (Lippincott: Philadelphia, 1969, pp. 17–22).

During wakefulness, a sequence of goal-oriented or *motivated behaviors* is displayed (a through h, Fig. **9.1**). If we take a complete behavioral episode, it can be divided into three sequential phases (I, F, C, Fig. **9.1**). First there is an *Initiation phase* that triggers the search for a specific goal object or task. In the case of hunger, *initiation stimuli* (IS, Fig. **9.1**) could include chemical signals related to low levels of blood glucose, the sight of an ad on TV for some tasty delight, or the smell of cooking dinner. Then there is the *Foraging phase* when an exploratory strategy is used to find the goal object. This is also referred to as the procurement phase. And finally, there is the *Consummatory phase* when the goal object is utilized and associated with pleasant or unpleasant sensations, and the behavioral episode comes to an end because of satiety mechanisms. Clearly, however, a behavioral episode can be interrupted at almost any time by a different initiation stimulus if it is strong enough. Certain sensations associated with the consummatory phase play a critical role in positive and negative reinforcement of behavior. These are pleasant or unpleasant feedback signals that are associated with particular behaviors and help to determine whether the particular behaviors are repeated or avoided in the future (Chapter 11, section on "Affect").

To recapitulate, it would seem that during sleep the cognitive system is active as dreaming occurs, whereas the sensory and somatic motor systems are somehow blocked. In contrast, during waking the cognitive and sensory systems modulate the output of the somatic motor system to produce behavior (Fig. 7.5 in Chapter 7). The rest of this chapter will delve further into the behavioral state system that controls the sleep-wake cycle, as well as the system that controls the level of arousal when awake. But first, it is illuminating to discuss a truly fascinating topic: circadian rhythms.

Circadian Rhythms: The Day-Night Cycle

Throughout the entire span of evolution, life has been subjected to a day-night cycle where the length of the day varies in an extremely precise way with the seasons every year. Thus, it may not come as a total shock to learn that many animals have evolved *endogenous clocks* that produce a rhythm of activity with a period of about 24 hours (the definition of circadian). In mammals, there is a tiny, compact group of neurons embedded in the hypothalamic visceromotor pattern generator network on either side of the third ventricle called the *suprachiasmatic nucleus*. Each nucleus produces a circadian rhythm of neuronal activity and together they determine the pattern of the sleep-wake cycle, and thus produce circadian rhythms in locomotor activity (walking around and foraging), eating and drinking, and a variety of more basic autonomic and endocrine responses. If a suprachiasmatic nucleus is removed from the brain and appropriately maintained in a dish, it can be kept alive for several days, and during that time it produces an endogenous circadian rhythm of activity.

In a very real sense, the suprachiasmatic nuclei are responsible for the fact that if people (or other animals) are placed in constant light or darkness (for weeks), they continue to show a sleep-wake cycle that is very similar to the one they display under normal conditions. There is, however, one curious twist—under constant lighting conditions, the time that people typically go to sleep is roughly a half-hour later each day. The biological circadian clock has a period of about 24.5 hours (not the astronomical 24 hours), so that under constant lighting conditions it begins to "free-run." Under these conditions the circadian rhythm begins to drift in a predictable way, whereas under normal conditions the rhythm is synchronized to the day-night cycle by information from the eye. One of the more surprising findings of the 1970s was that the retina, and thus the optic nerve, has a direct axonal input to the suprachiasmatic nucleus. This input provides information about environmental luminance (very roughly, time of day, and even season of the year in terms of day length) to it.

Something incredible happens when the suprachiasmatic nuclei are lesioned—something that could never have been predicted before the experiments were actually conducted in the 1970s. Animals immediately lose their usual sleep-wake cycle (Fig. **9.3**). Instead of sleeping more or less continuously for about 12 hours, and then staying awake for the next 12 hours (with an occasional nap), there are alternating periods of sleep and waking that last for an hour or so throughout the 24 hour period. There is still a sleep-wake cycle, but its periodicity is much shorter. As a matter of fact, it would seem that this is the natural period for the sleep-wake cycle, and that the suprachiasmatic nuclei somehow impose a roughly 24-hour period on it—somehow convert an approximately 1-hour rhythm to an approximately 24-hour rhythm. Naturally, this leads to a complete reorganization of the animal's behavior. For example, eating and drinking in lesioned animals are distributed evenly across the 24-hour period, instead of being concentrated in the continuous 12-hour period that the intact animal is awake each day. The extended periods of restlessness displayed by patients with Alzheimer disease may be due in part to pathological lesions of their suprachiasmatic nuclei.

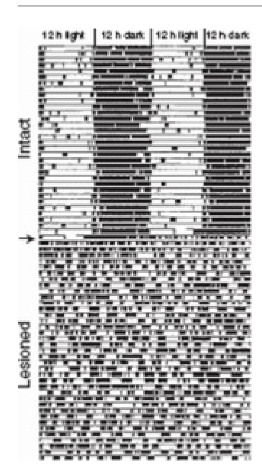






Figure 9.3
The pattern of locomotor activity in a rat maintained on a 12-hour light-dark cycle, before (above the arrow) and after (below the arrow) bilateral lesions of the suprachiasmatic nuclei. The data are double plotted for ease of interpretation. In other words, each horizontal line shows the preceding day and the new day. Note that in the intact animals, locomotor activity (dark bins) is confined to the period when it is dark (rats are nocturnal animals). In contrast, after suprachiasmatic nucleus lesions the normal rhythm is abolished and locomotor activity is spread more or less evenly over the 24-hour period. Adapted with permission from R.Y. Moore, Circadian timing, in: M.J. Zigmond, F.E. Bloom, S.C. Landis, J.L. Roberts, and L.R. Squire (eds.), *Fundamental Neuroscience* (Academic Press: San Diego, 1999, pp. 1189–1191).

Quite recently there have been major breakthroughs in understanding the molecular basis of circadian rhythm generation in suprachiasmatic neurons, and very surprisingly many other cells of the body. The key to this advance was the identification of fruit fly mutants with altered daily rhythms. Characterization of the affected genes led to the identification of a group of genes whose protein products are involved in a complex feedback program of gene expression changes with a circadian pattern—a pattern that leads to circadian changes of neuronal electrical activity in the suprachiasmatic nucleus.

Reproductive Cycles

Many animals show a reproductive cycle, which tends to maximize the production and survival of offspring. From the historical perspective of evolution, it is the single most important bodily function, because without it the species could not survive in nature. It would become extinct. In the stickleback fish that Tinbergen analyzed (Fig. 8.10 in Chapter 8) the reproductive cycle is seasonal—it occurs once a year and is timed so that offspring are born during the spring. By way of contrast, women during their fertile years show an approximately lunar cycle that they go through 12 or 13 times a year, and female rats have an even shorter cycle that lasts only 4 or 5 days. In all three species the peak of the reproductive cycle occurs around the time of ovulation, which is actually triggered in the brain—by neural activity in the GnRH neuroendocrine motor neuron pool in and near the rostral hypothalamus (Figs. 8.11, 8.13–8.15 in Chapter 8). These motor neurons cause a *surge* of anterior pituitary gonadotropic hormone secretions that in turn lead to ovulation and the secretion of gonadal sex steroid hormones.

It is these gonadal steroids (estrogens in females and androgens in males) that are responsible for activating reproductive behaviors in males (Fig. 8.18 in Chapter 8) and females. They do this by entering the brain, where they modify gene expression related to neurotransmission in neural networks that mediate reproductive behavior—in essence activating these networks for specific functions like seeking out a mate and copulation. There is a sexually dimorphic network in the brain—one that is anatomically distinct like the genitalia and secondary sexual characteristics of the body—and its state is controlled by estrogens and androgens secreted into the blood from the gonads (see Chapter 12, section on "Cycles").

The basic idea behind these physiological and behavioral aspects of the reproductive cycle is shown beautifully in the rat, where they have been subjected to intense experimental analysis over the last century. Let's start with a very simple behavioral measure: the amount of walking around (locomotion or "activity") displayed by an animal. When this is measured in a female rat before puberty, it is at a relatively low level, which is about the same every day (Fig. **9.4**). However, when she reaches puberty, which is defined as the day she exhibits her first effective gonadotropin surge, she runs around a lot and actually looks for a male to copulate with. She is in "heat" for about a day just before, during, and just after she has ovulated and is thus fertile. In the time before she had ever ovulated, and during the 3 days after ovulation, she displays no reproductive interest in males—who in fact are actively avoided and vigorously defended against in the event of a sexual advance.

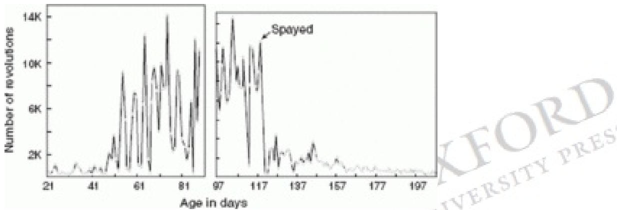


Figure 9.4
Locomotor activity (number of revolutions) as a function of age in female rats. Note first that locomotor activity is quite low until about day 50, when the animal undergoes puberty and displays its first estrogen surge and ovulatory cycle. On the day of ovulation, the animal is in behavioral "heat" and displays a dramatic increase in locomotor activity, which is directed toward finding and attracting a mate. Then note that there is a major peak of locomotor activity every 4 days, the length of the estrous cycle in this animal. Finally, note that on day 119 the animal was ovariectomized (spayed). The estrous cycle is abolished immediately, along with the 4-day cycles of locomotor activity. The cycle can be restored by endogenous treatments with estrogen. Adapted with permission from S.A. Barnett, *The Rat: A Study in Behavior* (Aldine: Chicago, 1963, p. 115).

This 4- or 5-day cycle of ovulation and behavioral heat goes on relentlessly until menopause, or until the gonads are removed (or their estrogens are blocked pharmacologically, say for birth control purposes). The beauty of this model is that we know estrogens are responsible because the cycle can be restored in castrated animals by estrogen replacement. After this simple procedure, behavioral heat is displayed about 8 hours later, presumably the time it takes for estrogen to modify a specific (incompletely understood) gene expression pattern in the sexually dimorphic brain network that is required to produce the foraging and solicitous behaviors associated with heat (Fig. **9.4**). By contrast, sexually mature male rats do not show a cycle of testosterone secretion. In essence, they are always interested in female rats, especially those in heat, who are probably secreting powerful pheromones. As in females, gonadal steroids contribute a great deal to "interest" in the opposite sex. In male rats, the sex drive is severely reduced by castration and is restored when they are treated with physiological replacement doses of testosterone.

The important generalization here is that the reproductive cycle plays a fundamental role in organizing behavior patterns, similar to (although not as dramatic as) that imposed by the sleep-wake cycle. Clearly, different behavioral states are associated with extremes of the reproductive cycle, and fluctuating levels of gonadal steroids play an important role in establishing these behavioral states. The reason for dealing with this topic here is that lesions of the suprachiasmatic nucleus abolish the normal reproductive cycle in rats, just as they abolish the normal sleep-wake cycle. Somehow, the circadian signal from the suprachiasmatic nucleus is converted in rats and mice to a 4- or 5-day signal destined for the gonadotropin surge generator. This conversion probably takes place in the anteroventral periventricular nucleus of the hypothalamus, which receives an axonal input (a projection) from the suprachiasmatic nucleus and in turn projects to the GnRH neuroendocrine motor neuron pool that controls gonadotropin secretion from the pituitary gland. Lesions of the anteroventral periventricular nucleus also abolish the reproductive cycle in rats.

Sleep-Wake Cycles

We noted earlier in the chapter that total removal of the hypothalamic master circadian clock (the suprachiasmatic nuclei) produces alternating bouts of sleep and wakefulness that last about an hour to an hour and a half throughout the 24-hour period of each day (Fig. **9.3**). The neural mechanism (whether an individual cell group or a specialized network) responsible for generating this fundamental pattern of sleep and wakefulness is not known. Obviously, then, it is unclear how the suprachiasmatic nuclei convert this fundamental pattern into the typical situation where a person or animal sleeps more or less continuously for 8 to 12 hours a day and is awake the rest of the time.

Nevertheless, there is good experimental reason to suspect that the fundamental sleep-wake generator or clock resides in rostral (oral) regions of the pontine reticular nucleus. Furthermore, this same general region is responsible for the generation of REM sleep, or at least several major features characteristic of REM sleep. For example, cholinergic neurons in the pedunculopontine tegmental nucleus project to the thalamus and appear to be critical for generating the ponto-geniculo-occipital (PGO) spikes characteristic of the EEG in REM sleep, and other pontine neurons with caudally directed projections appear to be responsible for the muscle atonia (relaxation) characteristic of REM sleep. This occurs at least in part via an excitatory (glutamatergic) projection to the ventral medulla, which in turn sends a caudally directed inhibitory (at least partly glycinergic) projection to spinal motor neuron pools. It is intriguing to note that the bouts of sleep and wakefulness in animals with suprachiasmatic nucleus lesions are about an hour or so long (Fig. **9.3**), as are bouts of REM and deep sleep (Fig. **9.2**). These facts hint at the existence in the pons of a fundamental behavioral state rhythm generator, with a period of about 90–120 minutes, that mediates both the underlying sleep-wake cycle and the REM/deep sleep cycle.

There is extensive evidence that certain specialized cell groups in the brainstem control the output of the fundamental behavioral state rhythm generator in the pons, control levels of arousal during wakefulness, and/or control the various stages of the sleep cycle itself. However, at this point in time the extent to which these cell groups simply modulate behavioral state rhythm generators—as opposed to forming integral parts of the rhythm generator networks themselves—remains unclear. For the sake of convenience, then, we shall now consider a series of interesting cell groups in the brainstem that are characterized by the expression of a signature neurotransmitter (often a biogenic amine), by the elaboration of relatively widespread axonal projections, and by apparent involvement in modulating or controlling behavioral state.

Modulating Behavioral State

In the early 1960s two young Swedish neuroscientists, Annica Dahlström and Kjell Fuxe, carried out a highly original series of neuroanatomical studies with a novel histochemical method that had just been developed by their mentors, Bengt Falck, Arvid Carlsson, and Nils-Åke Hillarp, for the demonstration of *biogenic amine-containing neurons*. Dahlström and Fuxe described in detail the overall organization of several neural systems that previously had been unsuspected, and that were so unusual it took many years to convince the more skeptical neuroanatomists (who almost by trade are very conservative) of their reality.

One neural system contains norepinephrine, the same neurotransmitter used by the sympathetic division of the autonomic motor system (see Chapter 8, section on “The Autonomic Motor System”). One *noradrenergic cell group* in particular stood out: the *locus ceruleus*. It soon became clear that neurons in this cell group of the pontine central gray send axons to innervate virtually the entire central nervous system—from the caudal end of the spinal cord, to the cerebellum and brainstem, to the entire cerebral cortex—in a seemingly diffuse, rather nonspecific way. The locus ceruleus had been discovered almost 200 years earlier in the human brain by the French neuroanatomist Félix Vicq d’Azyr (1746–1794) because it is a tiny but obvious blue location under the floor of the rostral fourth ventricle (Fig. **9.5**). But in hindsight no one in the meantime had even a clue as to its true connections and neurochemistry—it almost seems to form a sympathetic ganglion in the brainstem. Needless to say, it has now been implicated in a broad range of functions. However, it does seem safe to conclude that it plays a role in the processing of all novel stimuli during the waking state, and that it also plays an important role in switching between certain parts of the sleep-wake cycle. In rats the locus ceruleus is a virtually pure population of about 1600 noradrenergic neurons. Other central noradrenergic cell groups are all restricted to the pons and medulla and most of them appear to have more specialized functions than the locus ceruleus, functions especially related to the central autonomic control network.

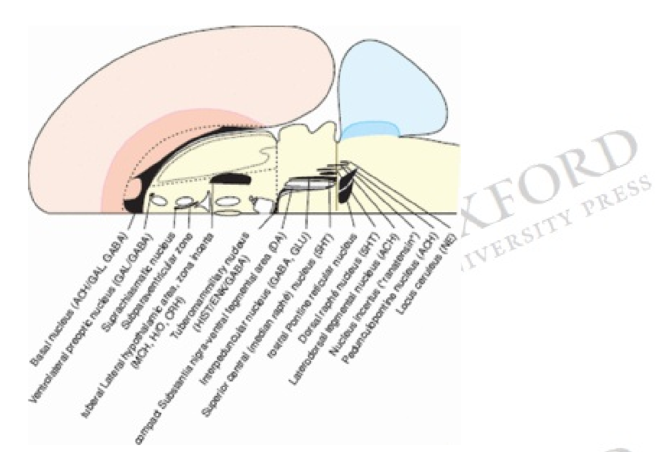




Figure 9.5
Major cell groups associated with the behavioral state control system are shown in black on this flatmap of the rat central nervous system. The behavior control column (see Fig. 8.11 in Chapter 8) is outlined in white. Key for neurotransmitters: ACH, acetylcholine; CRH, corticotropin-releasing hormone; DA, dopamine; ENK, enkephalin; GABA, gamma-amino butyric acid; GAL, galanin; GLU, glutamate; H/O, hypocretin/orexin; HIST, histamine; MCH, melanin-concentrating hormone; NE, norepinephrine; 5HT, serotonin.

A second system characterized by Dahlström and Fuxe uses serotonin as a neurotransmitter, and the neurons involved are found in the midbrain and pons—mostly in and around a group of nuclei that had been described earlier, but had no known function. These are the *raphé nuclei* that lie in and near the midline of the adult brainstem. The two largest groups of *serotonergic neurons* are centered in the midbrain (Fig. 7.5 in Chapter 7), just rostral to the locus ceruleus, and are known as the *dorsal nucleus of the raphé* and the *superior central nucleus (median nucleus of the raphé)*. These nuclei also have very widespread, seemingly diffuse, projections throughout much of the central nervous system, and they also play an important role in modulating or controlling various aspects of behavioral state.

A third system characterized by the two Swedes was centered in the ventral midbrain and uses dopamine as a neurotransmitter (Fig. 7.5 in Chapter 7). Unlike the noradrenergic and serotonergic systems just discussed, its projections are mostly rostrally directed. One specialization of this system is centered in the *compact part of the substantia nigra*, and its axons primarily innervate the dorsal striatum (part of the endbrain cerebral nuclei). This *dopaminergic pathway* degenerates in Parkinson disease, and systemic treatment with the dopamine precursor L-dopa alleviates patient's tremors and inability to initiate behaviors, at least during early stages of the disease. The other specialization of the system is centered in the adjacent *ventral tegmental area*, and so-called *retrorubral area*, and it has more widespread rostrally directed projections to the ventral striatum, prefrontal cortex, and hippocampal formation. Dahlström and Fuxe referred to the previously unknown dopamine neurons in these areas as the A8 and A10 cell groups, respectively. The dopaminergic compact part of the substantia nigra was called the A9 cell group.

The ventral tegmental area has been implicated in regulating levels of locomotor behavior (behavioral arousal during goal-oriented behaviors) and thus in subsequent mechanisms of reward and positive reinforcement. The differential roles of dopaminergic and nondopaminergic (probably GABAergic) neurons in the ventral tegmental area are not yet entirely clear. However, it seems possible that the former are involved in reward-related mechanisms, whereas the latter are involved in regulating locomotor behavior. This would be similar to the dopaminergic (compact) and nondopaminergic (reticular) parts of the adjacent substantia nigra.

Thus, Dahlström and Fuxe laid out the basic neuroanatomy of three neurotransmitter-coded brainstem systems that are definitely related to controlling behavioral state in one way or another (although the details are still not resolved). Since then a number of other nearby cell groups with similar functions have been identified (Fig. 7.5 in Chapter 7). For example, in the previous section of the chapter we discussed a *cholinergic cell group* centered in the *pedunculopontine nucleus* that is critically involved in modulating thalamocortical and other systems in relation to behavioral state, especially associated with REM sleep. Furthermore, a dorsally adjacent cholinergic cell group that lies next to the locus ceruleus in the pontine central gray has very widespread, seemingly diffuse, projections. This is the *laterodorsal tegmental nucleus*, and it has also been implicated clearly in the modulation of behavioral state. And finally, the obscure *nucleus incertus* should be mentioned. It also lies in the pontine central gray near the locus ceruleus, dorsal raphé, and laterodorsal tegmental nucleus. It is highly interconnected with two other brainstem midline nuclei (superior central and interpeduncular) and all three together project massively to forebrain systems associated with the prefrontal cortex and hippocampal formation. This midline trio of brainstem nuclei almost certainly plays a major role in behavior prioritization during the waking state.

As we move rostrally, we come to the lateral zone of the hypothalamus, which has often been thought of as the rostral end of the brainstem reticular formation. There are two especially interesting regions here. First we have the *tuberomammillary nucleus*, which is a thin collection of neurons that surrounds the mammillary body like a cradle. These neurons use *histamine* as one of their neurotransmitters (GABA is another one) and their axons have very widespread, seemingly diffuse, projections to most parts of the brain. They are the only neurons in the brain that synthesize histamine for use as a neurotransmitter, and the drowsiness associated with antihistamines is thought to result from interfering with their normal function.

The second interesting feature of the lateral hypothalamus in this context is the presence of three separate though intermixed neuron populations dorsally at the level of the ventromedial and premammillary nuclei (Fig. 7.5 in Chapter 7). All three populations appear to have very widespread projections to many parts of the central nervous system, including the brainstem, spinal cord, and cerebral cortex. One cell group uses the peptide *melanin-concentrating hormone* (MCH) as one of its neurotransmitters, another uses the peptides *hypocretin/orexin* and *dynorphin* as several of its neurotransmitters, and the other uses corticotropin-releasing hormone (CRH) as one of its neurotransmitters under certain conditions like axorexia. It has long been thought that the lateral hypothalamus plays an important role in modulating behavioral state, but this was shown dramatically with the discovery that mutations in the hypocretin/orexin gene, or in the gene for its receptor, cause narcolepsy, where animals and people have difficulty staying awake. This is the only population of neurons in the brain that expresses the hypocretin/orexin gene. Recent evidence indicates that interconnections between the tuberomammillary nucleus, lateral hypothalamic area, and a tiny differentiation called the ventrolateral preoptic nucleus are involved in switching between sleep and wakefulness, presumably in concert with the rostral pontine reticular nucleus.

Finally we come to the cerebral or basal nuclei of the endbrain. Here we encounter a population of cholinergic neurons that has a topographically organized, though widely overlapping, projection to the entire cerebral cortical mantle. In the 1960s it was associated with the primate *basal nucleus of Meynert*, which had been discovered a century earlier. The cholinergic neurons are distributed irregularly, sometimes clumped and sometimes widely spaced, throughout the ventral pallidum and medial septal complex, and then become sparser in the dorsal pallidum and even in parts of the striatum. The precise function of these neurons is unclear, though they degenerate in Alzheimer disease and are thought to play a role in learning and memory mechanisms, and in the modulation of behavioral state. It is now known that the so-called basal forebrain projection to cortex involves other neuron types as well.

In summary, anatomically and neurotransmitter distinct neuronal cell groups stretching from the pons and midbrain through the hypothalamus to the cerebral nuclei play a critical role in modulating behavioral state. It seems clear that each of the neuron groups has a specialized function—although exactly what those functions are remains to be determined—and that they are highly interconnected to form an exceedingly complex neural network. Presumably, specific patterns of activity within the network determine not only behavioral state, but also levels of arousal within particular states. This network can be thought of as separate from the purely sensory and motor systems, as well as from the cognitive system of the cerebral hemispheres (Fig. 7.5 in Chapter 7). In a gross anatomical sense it is roughly adjacent to the behavior control column discussed in Chapter 8, section on “Pattern Initiators and Controllers” (Figs. 8.11 [in Chapter 8] and 9.5 [in Chapter 9]).

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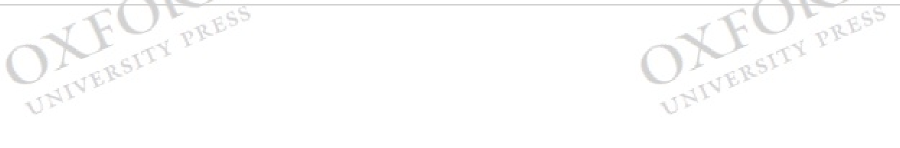
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Brain Architecture (2 ed.): Understanding the Basic Plan

Larry W. Swanson

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The Cognitive System : Thinking and Voluntary Control of Behavior

Chapter: The Cognitive System
Author(s): Larry W. Swanson
DOI: 10.1093/med/9780195378580.003.1098

> *"Thus there remains for exposition what it is that initiates voluntary movements, sensations, and that Reigning Soul, by which we imagine, meditate, and remember. To this task the present book is devoted."*
>
> Andreas Vesalius (1543)
>
> *"I divide the functions of the brain into two classes:* vis., *affective and intellectual; and, in harmony with this physiological division, I recognize two kinds of cerebral parts. The anterior pyramidal bodies [pyramids] I consider the rudiments of such as belong to the intellectual operations; and the other bundles of the medulla oblongata…which run across the annular protuberance [pons] to communicate with many of the cerebral masses, as the roots of those that pertain to the affective manifestations… This separation into two systems of parts is very evident from the medulla oblongata upwards, as far as the pretended optic thalami [interbrain] and striated bodies [cerebral nuclei] in man and the mammalia."*
>
> Gasper Spurzheim (1826)
>
> *"The complexity of the nervous system is so great, its various association systems and cell masses so numerous, complex, and challenging, that understanding will forever lie beyond our most committed efforts."*
>
> Santiago Ramón y Cajal (1909)

The cerebral cortex is the crowning glory of evolution. It is the part of the nervous system that is responsible for thinking. Quadriplegics, who tragically have had their spinal cord disconnected from their brain, can think just fine, and so can people born without a cerebellum. But extensive damage to the cerebral cortex profoundly interferes with cognition. The cerebral cortex is the organ of thought. Can the organ of thought ever understand itself? Will we ever understand the physical basis of thought? Can we ever discover the fundamental organizing principles of the cerebral cortex network? What is the biology of consciousness? If nothing else—how far have we come in our attempts to understand the brain substrates of thinking?

It was not so long ago that even trying to answer this question was dangerous. Franz Joseph Gall (1758–1828) was the first physician-neuroscientist to argue that thinking takes place in the gray matter of the cerebral cortex, and that different aspects of cognition are elaborated in different regions of its gray matter. However, in 1802 the German emperor Francis the First forbade Gall to lecture publicly or privately about this topic, on the grounds that it was materialistic and thus antireligious. Three years later Gall was banished from his native land forever and began traveling through Europe, finally settling in Paris in 1807. This is how his monumental four-volume *Anatomie et physiologie du système nerveux…*, much of which was written in collaboration with his younger colleague Johann Gaspar Spurzheim (1776–1832), came to be published in Paris rather than Vienna between 1810 and 1819.

Gall and Spurzheim also postulated that if a particular gray matter region is unusually large, and the corresponding mental function correspondingly overdeveloped, this would be reflected in an expansion or bump in the overlying region of skull. This assumption spawned the pseudoscience of phrenology, whose practitioners, led initially by Spurzheim himself, tried to determine people's mental gifts as well as deficiencies by analyzing the exact shape of the skull. But even in contemporary France there was widespread opposition to the idea of functional localization within the cerebral cortex itself. This hesitation was based largely on the experiments of Flourens, mentioned in Chapter 7. He used the ablation method in the 1820s to conclude that whereas the cerebral hemispheres are indeed the seat of intelligence and sensation, they are not functionally partitioned. Instead, he interpreted his results to indicate that the special senses and intellectual faculties are represented or distributed throughout the hemispheres. This view was not significantly eroded until the 1860s when the pioneering work of Paul Broca (1824–1880), Gustav Fritsch (1837–1927), Eduard Hitzig (1839–1907), Hermann Munk (1839–1912), and David Ferrier (1843–1928) began to establish cerebral localization for speech, motor control, and the various sensory modalities. Today, cognitive neuroscientists are using functional magnetic resonance imaging (fMRI) studies on living human brains to measure individual differences in cortical localization for every conceivable psychological factor. The basic principles underlying phrenology—cortical localization of function, and individual differences in cortical specialization—are being exploited as never before.

Cerebral Cortex Regionalization

In Chapter 6 we found that each cerebral hemisphere (also known as cerebrum, endbrain, or telencephalon) may be divided into two very different parts. One lies more dorsally and is a layered, sheet-like tissue known as the cerebral cortex or pallium. The other part lies more ventrally and overall does not have a laminated appearance. It has

been referred to variously as the basal ganglia, basal nuclei, or cerebral nuclei. The cerebral cortex is undoubtedly the best place to start because there is widespread agreement about its fundamental organization, which is relatively straightforward.

The basic division between cerebral cortex and cerebral nuclei becomes evident in the early embryo at the five-vesicle stage of the neural tube illustrated in Figure 5.14 in Chapter 5. Here the cerebral hemisphere has the simple shape of a contact lens or slightly flattened hemisphere, with the transition between future cerebral cortex and cerebral nuclei indicated by a shallow internal groove, the corticostriatal sulcus (Fig. **10.1**). As the mammalian cerebral cortex develops further, it evaginates or balloons out tremendously (Fig. **10.2**) and eventually becomes corrugated or folded to a greater or lesser extent in different species. Mechanisms underlying the development of cortical folding into gyri separated by sulci (and deeper fissures) are not established, but it does mean that much more cortical surface area may be squeezed into the limited volume created by the skull. This folding of the cortical sheet is obvious in the Frontispiece brains and in Figure **10.3**. It is responsible for the fact that about two-thirds of the human cortical sheet (which has a surface area of about one square foot per hemisphere) is buried below the outer, readily visible surface of the hemisphere next to the skull.

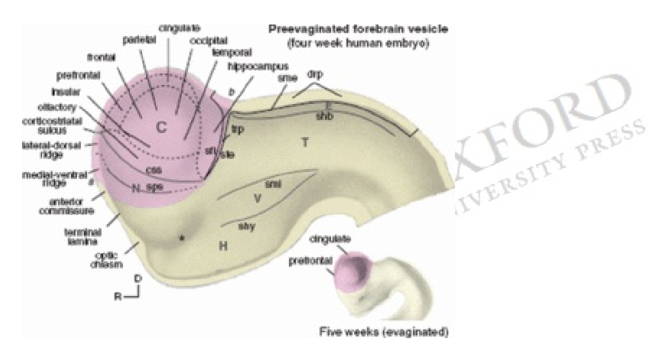




Figure 10.1
The large drawing shows the right forebrain vesicle of the 4-week human embryo, with a fatemap superimposed on the endbrain (cerebral hemisphere or just cerebrum). Note that the cerebrum will be divided into cortex (C) and nuclei (N). This is an instructive stage because the hemisphere has not yet begun to evaginate (see smaller drawing where it has just begun, and Fig. **10.2** where it is more advanced), so a qualitative fatemap of cortical regionalization is easy to plot. Key: *a-b*, ends of a line that separates endbrain and interbrain components of the forebrain vesicle, the prospective interventricular foramen on the inside and the hemispheric sulcus on the outside; css, corticostriatal sulcus; D-R, dorsal and rostral; drp, interbrain roof plate; E, epithalamus; f, a line indicating the approximate plane in Figure **10.2**; H, hypothalamus; sfi, fimbrial sulcus; shb, habenular sulcus; shy, hypothalamic sulcus; sme, sulcus medullaris; smi, middle interbrain sulcus; sps, striatopallidal sulcus; ste, sulcus terminalis; T, thalamus; trp, endbrain roof plate; V, ventral thalamus; *, optic sulcus of optic vesicle. Adapted with permission from L.W. Swanson, Cerebral hemisphere regulation of motivated behavior, *Brain Res*., 2000, vol. 886, p. 117.

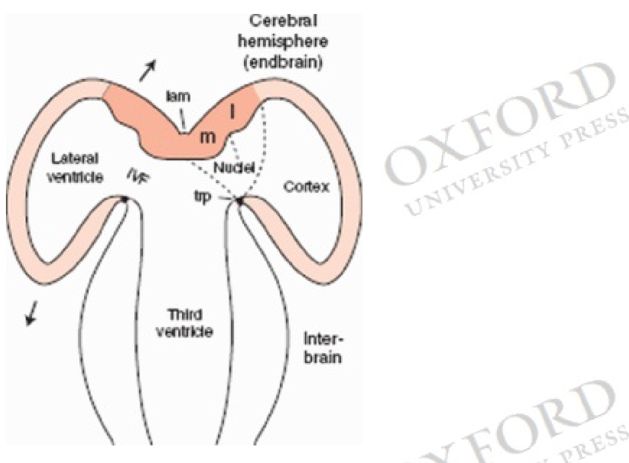




Figure 10.2
Schematic frontal section through the forebrain vesicle as the cerebral hemisphere is beginning rapidly to evaginate and expand, as indicated by arrows (more detail than Fig. 5.14). Key: IVF, interventricular foramen (of Monro); l, lateral or dorsal ventricular (striatal) ridge, also called lateral ganglionic eminence; lam, terminal lamina; m, medial or ventral ventricular (pallidal) ridge, also called medial ganglionic eminence; trp, endbrain roof plate. Adapted with permission from L.W. Swanson, *Brain Maps: Structure of the Rat Brain* (Elsevier: Amsterdam, 1992, p. 33).

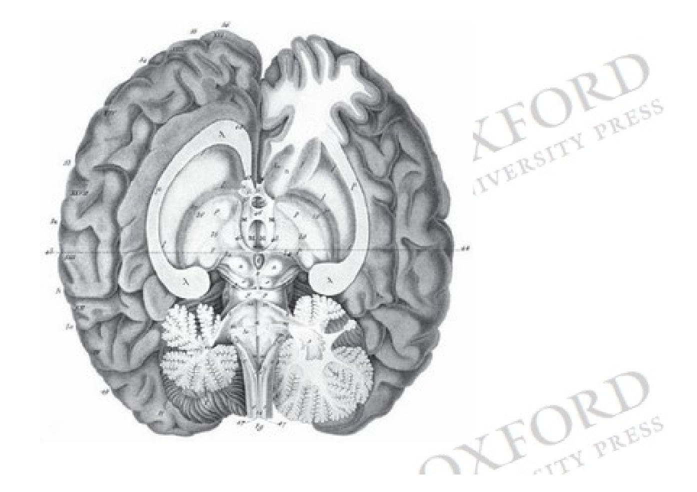




Figure 10.3
In this dissection the human brain was partly bisected from above and opened up like a book—so one is viewing the medial surfaces of the cerebral hemispheres and the dorsal surface of the brainstem. In addition, the frontal pole of the right cerebral hemisphere was sliced off to reveal the characteristic pattern of gray matter and white matter associated with the cerebral cortex. The deep cerebellar gray (the dentate nucleus) is nicely illustrated, embedded within the cerebellar white matter (arbor vitae) on the right side. From F.J. Gall and J.C. Spurzheim, *Anatomie et physiologie du système nerveux en général et du cerveau in particulier* (Schoell: Paris, 1810–1819, plate VI).

The point of this discussion is that the adult cerebral cortex is a sheet that can be flattened, at least in principle. Topologically it can be thought of as a flat sheet that is attached along its lower or ventral border to the cerebral nuclei, a relationship that is crystal clear in the early embryo (Fig. **10.1**). This basic relationship does not change as the embryonic cerebrum develops into the adult. So it is possible to divide up the cortical sheet into structurally and functionally different regions, like a map of Europe can be divided into a number of different countries. This division or regionalization scheme has emerged from a vast amount of research in the century and a half since Broca, Fritsch, Hitzig, Munk, and Ferrier began the work mentioned earlier. And like maps of Europe over the same period of time, boundaries between regions have changed considerably and have been subject to different interpretations by different parties. As more is learned about cerebral organization, the map is bound to evolve in the future.

The first hint of structural regionalization came from the research of an Italian medical student, Francesco Gennari (1750–1794), who in 1776 noted the presence of a distinct white matter layer in caudal regions of the freshly sliced human cerebral cortex. As we shall soon see, it became clear many years later that the famous “stripe of Gennari” is a characteristic feature of one particular human cortical area—the primary visual area of the occipital lobe (or region), and more specifically layer 4 of this area, which is also known as the striate area because of the characteristic stripe. A few years earlier the great biologist Albrecht von Haller (1708–1777) began referring to large expanses of cortex with reference to the bones of the skull overlying them: hence the frontal, parietal, occipital, and temporal regions or lobes. Then, beginning with Theodor Meynert (1833–1898) in the 1860s, neuroanatomists began producing a succession of maps that more or less systematically describe structural regionalization throughout the cortical sheet or mantle based on histological criteria. The most famous and enduring cortical maps were generated by Korbinian Brodmann (1868–1918), whose 1909 book on the topic is an intellectual tour de force and great classic of neuroscience. Based on how neuron cell bodies tend to form layers in different regions of the cortical mantle, Brodmann recognized about 50 distinct cortical *areas* in mammals, which he numbered in an arbitrary way (Fig. **10.4**). The topological relations of these areas are illustrated on a cortical flatmap in Figure **10.5**.

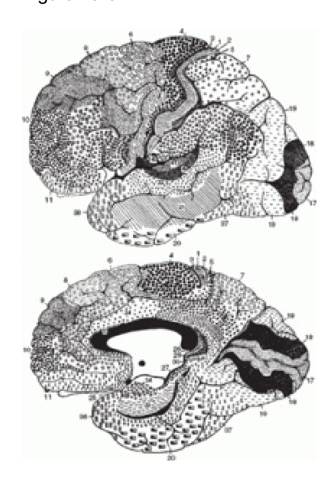




Figure 10.4
Brodmann's regionalization maps of the human cerebral cortex as projected schematically onto the lateral (top, left hemisphere) and medial (bottom, right hemisphere) aspects. Each cortical area is indicated by a different pattern of symbols and a different number. He used this scheme to compare cerebral cortical regionalization in nine different mammalian species. From K. Brodmann, *Vergleichende Localisationslehre der Grosshirnrinde in ihren Prinzipien dargestellt auf Grund des Zellenbaues* (Barth: Leipzig, 1909, p. 131).

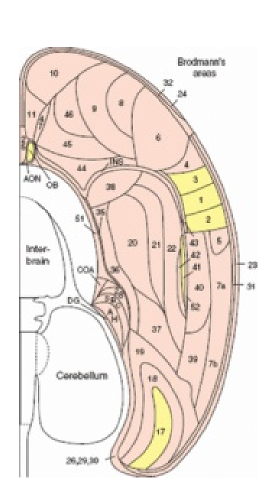





Figure 10.5
A topological representation of Brodmann's regionalization of the cerebral cortex (light red) into areas is shown on this flatmap of the human brain (see Figs. **10.3** and **10.4**). Primary sensory cortical areas are indicated in yellow. Compare with Figures 6.7 and **10.1**. Key: 1–3, somatic sensory; 17, visual; 41, auditory; AH, Ammon's horn; AON, anterior olfactory area, COA, cortical amygdalar area; DG, dentate gyrus; INS, insular area; OB, olfactory bulb; SBC, subicular complex. Adapted with permission from L.W. Swanson, Mapping the human brain: past, present, and future, *Trends Neurosci*. 1995, vol. 18, poster accompanying p. 471.

Whether acknowledged or not, all critical work done in the last century on cerebral cortical structure and function is derived from the maps produced by Brodmann. What has been done in the meantime is to assign functional significance to many of the areas, and often to parcel the original areas even further. Although there is a great deal of controversy about details, one appealing hypothesis views the cortical mantle as divided broadly into *motor areas, unimodal sensory areas, and polymodal association areas*

where more than one sensory modality converge. In a provocative 1970 article Edward Jones and Thomas Powell suggested that information from each sensory modality follows a similar progression of connections through cortex, at first separate and then eventually converging in polymodal association areas.

First, sensory information reaches a primary unimodal sensory area (illustrated by yellow shading in Fig. **10.5**). Then it is relayed to one or more adjacent, corresponding unimodal sensory association areas, where more complex processing of the particular mode of sensory information takes place—as well as to one or more motor-related areas in the frontal region. Then, from each unimodal association area there are axonal outputs to adjacent association areas and to other motor-related areas in the frontal region as well. Eventually, unimodal association areas connect to polymodal association areas, where information from two or more sensory modalities converges. Polymodal association areas in turn also connect to motor areas, as well as back to unimodal sensory areas. For example, Brodmann's area 17 would be considered the primary visual area, his areas 18 and 19 would be considered unimodal visual association areas, the inferior temporal area (area 20) and the hippocampal formation would be considered polymodal association areas, and areas 4, 6, and 8 would be considered primary and supplementary motor cortical areas.

While it has been found very useful to think about cortical function in this way—by following the course of a particular sensory modality after it reaches the primary cortical area—the actual situation is much more complex than this. Every cortical area receives information from a specific nucleus or more generally set of nuclei in the thalamus, as well as a variety of rostrally directed inputs from the behavioral state control system (see Chapter 9, section on “Modulating Behavioral State” and Fig. 9.5). In a real sense, then, each cortical area is under constant parallel control by rostrally directed inputs, even though serial processing of particular sensory inputs may be taking place simultaneously through particular intracortical pathways. Then there is the actual dynamics of information processing within what is obviously a network of connections between the various cortical areas—whose principles are very far from understood.

At a very basic level, though, the connections forming this intracortical network may be divided into two classes: association and commissural. *Association connections* are established between cortical areas within the same hemisphere, whereas *commissural connections* are formed between cortical areas in the right and left hemispheres. Commissural tracts crossing the midline and thus interconnecting the two hemispheres include the anterior commissure, the great cerebral commissure (corpus callosum), and the hippocampal commissures. The detailed organization of intracerebral connections may well lie beyond the limits of human comprehension.

Cortical Cellular Organization

Cortical lamination patterns have been referred to again and again. What are they? The feature that Brodmann and many others have exploited is the distribution of neuron cell bodies within the cortical sheet. In the 1890s Franz Nissl (1860–1919) perfected a stain to display very clearly the location, size, and shape of neuron cell bodies in histological sections of the nervous system, and his method has become perhaps the most widely used in neuroanatomy for its simplicity, reliability, and utility. This is the method that Brodmann applied to the cerebral cortex of a wide variety of mammals. In essence, he recognized about 50 different or distinct lamination patterns in the cerebral cortex. At the most general level, he divided them into two classes. One class supposedly passes through a clear six-layered stage during development, and he referred to it as *homogenetic cortex*. The other class does not pass through a six-layered stage during development, and he referred to it as *heterogenetic cortex*. A few years later, in 1919, Oskar Vogt (1870–1959) and Cécile Vogt (1875–1962) applied the terms *isocortex* and *allocortex* to the homogenetic and heterogenetic cortices, respectively, and the Vogt's terms are preferred today. Other popular terms are neocortex (for isocortex), and paleo- and archicortex (together for allocortex), but they are based on unfounded evolutionary arguments originating near the end of the nineteenth century.

Perhaps the best example of different isocortical lamination patterns involves the adjacent areas 17 and 18—primary visual and unimodal visual association areas, respectively. Figure **10.6** is a photomicrograph, taken from Brodmann's work, of a Nissl-stained tissue section cut perpendicular to the surface of the human cortex, with the border between areas 17 and 18 running down the middle. First note the six classical cell layers of isocortex in both areas. Next, examine layer 4 (IV). Throughout the isocortex it is characterized by small neurons, and for this reason it was long ago named the granular or granule cell layer. However, observe that in area 18 (right) layer 4 is relatively uniform from superficial (surface of the cortex at the outer edge of layer 1) to deep (toward the deep white matter below layer 6), whereas in area 17 (left) layer 4 is very clearly split into three sublayers, a, b, and c. Obviously, this expansion and differentiation of layer 4 has profound effects on the thickness of adjacent layers 3 and 5 in area 17. There is no doubt that the laminar distribution of neurons in areas 17 and 18 is quite different, although the differences appear to be quantitative variations on a qualitative six-layered scheme.

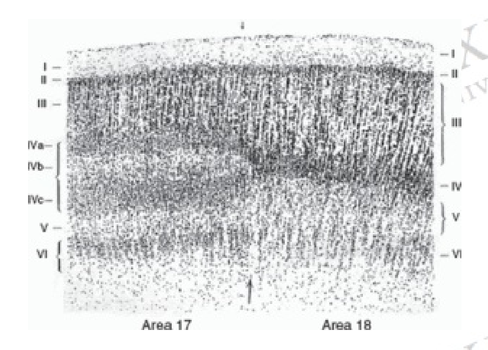


Figure 10.6
The cytoarchitecture of human unimodal visual cortex as seen in a photomicrograph of a Nissl-stained tissue section. Arrows indicate the border between area 17 (left) and area 18 (right). Layers of cortical gray matter are identified by the Roman numerals at either end. The lower arrow is in the deep white matter of the cerebral cortex. The outer surface of the cortex is at the top. From K. Brodmann, *Vergleichende Localisationslehre der Grosshirnrinde in ihren Prinzipien dargestellt auf Grund des Zellenbaues* (Barth: Leipzig, 1909, p. 32).

There are also clear, though perhaps more subtle, differences between the various primary sensory cortical areas. Figure **10.7** illustrates Cajal's interpretation of laminar differences between visual cortex and auditory cortex in the adult male human brain. Here Cajal has chosen to illustrate his findings with drawings of Nissl-stained sections rather than with photographs, which he virtually never used for neurohistology. Disregarding Cajal's alternative lamination numbering scheme (his layer 5 corresponds to Brodmann's layer 4), it is obvious that there are differences throughout the thickness of each cortical area. One can only assume that these differences are somehow responsible in part for the qualitative differences between visual and auditory sensations.

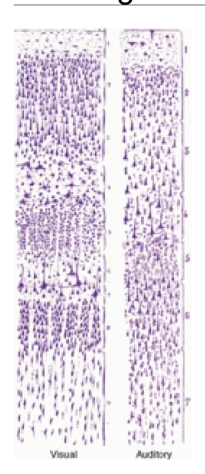






Figure 10.7
The cytoarchitecture of human visual and auditory cortex is compared in these drawings of Nissl-stained sections by Cajal. Note that Brodmann later used a different numbering scheme for the lamination pattern (see Fig. **10.6**, right half, for visual cortex). From S.R. Cajal, *Histologie du système nerveux de l'homme et des vertébrés*, vol. 2 (Maloine: Paris, 1911, pp. 603, 621).

Basically, structural neuroscientists have over the years attempted to determine how many different cortical areas they can distinguish on the basis of such differences in lamination patterns. Unfortunately, many of the distinctions that have been made are considerably subtler than those illustrated here, and some authors have argued that gradients rather than clear borders are found between certain adjacent "areas" of association cortex. Overall, the number of cortical areas distinguished by various investigators ranges from about 20 to 400.

Estimates of total neuron number in the human cerebral cortex on both sides of the brain range from roughly 3 to 14 billion. This is a lot of neurons by any account, and there may be on the order of 10 times as many glial cells. Fortunately, it seems reasonable to assume that most or all of these neurons fall into two broad classes: pyramidal neurons that have long projections, and stellate neurons that have local connections within a particular cortical area. This distinction was originally made in a brief, three-page report by Golgi in 1873. Here, in what is probably line for line the most important paper in the history of neuroscience, the young Italian physician reported a radically new method for staining individual neurons in their entirety. Based on its application, he discovered that contrary to conventional wisdom, dendrites do not anastomose with one another; he described accurately for the first time axon collaterals; and he divided all neurons (including those in cerebral cortex) into those with a short (intraregional) axon or those with a long (interregional) axon.

In the isocortex (Fig. **10.8**) there are very few neurons in layer 1, layers 2 and 3 are characterized by relatively small pyramidal neurons (along with interneurons), layer 4 consists almost entirely of local connection (granule or stellate) interneurons, and layers 5 and 6 are characterized by larger pyramidal neurons (along with interneurons). Interestingly, the smallest pyramidal neurons tend to be localized to layer 2, and they typically generate association connections to other cortical areas within the same hemisphere. Layer 3 pyramidal neurons tend to be somewhat larger, and they typically generate commissural connections to the opposite hemisphere, as well as association connections to the same hemisphere. The largest pyramidal neurons are found in layers 5 and 6, and they are responsible for generating most of the caudally directed cortical connections to the cerebral nuclei, brainstem (including the thalamus), and spinal cord.

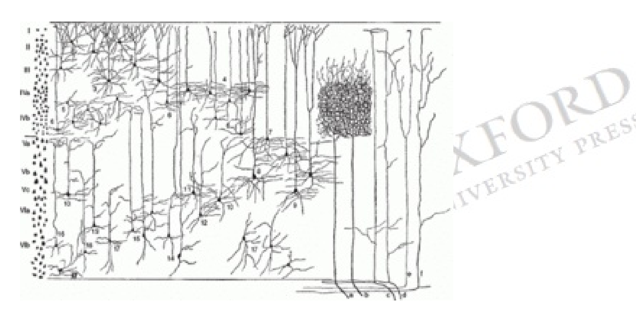




Figure 10.8
Some of the major neuron types (1–17) found in various layers (I–VIb) of the cerebral isocortex, along with the morphology of certain major classes of axons that enter the cortex to terminate (a–f). The cortical layers are identified with the Nissl stain, whereas neuron types and input axons are drawn from Golgi preparations. From a drawing by Raphael Lorente de Nó in: J.F. Fulton, *Physiology of the Nervous System* (Oxford University Press: London, 1938, p. 302).

This arrangement suggests that the lamination patterns characteristic of cerebral cortex are due to the differential distribution of pyramidal neuron subpopulations that are distinguished by different connection terminal fields—for example, association connections versus commissural connections versus caudally directed connections to the cerebral nuclei, brainstem, and spinal cord. Modern pathway tracing experiments bear this assumption out; they show that each cortical area subjected to careful analysis has a distinct pattern of connections to other regions of the central nervous system that are presumably generated by different subpopulations of pyramidal neurons—which are reflected in more or less obvious lamination patterns.

This arrangement also suggests a basic organization of isocortex into three "super layers": supragranular, granular (layer 4), and infragranular. Layer 4 is characterized by a dense input from the thalamus (Fig. **10.8**b), and much of the local output of layer 4 stellate interneurons is directed toward the supragranular layers. The supragranular layers of relatively small pyramidal neurons generate primarily intracortical outputs. In essence, the supragranular layers generate the immensely complex network of connections between cortical areas, and Cajal was perhaps the first to emphasize the possibility that this network is primarily responsible for thinking, learning, and memory. The supragranular layers also provide a major input to the infragranular layers of relatively large pyramidal neurons that generate most cerebral cortex output to other central nervous system regions. In other words, the infragranular layers are essentially the extrinsic output component of the cerebral cortex. According to this scheme for isocortex, infragranular layers execute the cognitive computations elaborated in supragranular layers—the infragranular layers are the predominant origin of voluntary control inputs to the motor system.

Cortical Outputs

As just mentioned, the majority of output connections from the isocortex arise from pyramidal neurons in the infragranular layers. Broadly speaking, these outputs seem to arise from three classes of pyramidal neurons. One class dominates layer 6 and projects to the thalamus. Another class dominates in superficial layer 5 and is characterized by an input to the striatal component of the cerebral nuclei. And the other class dominates in deep layer 5 and projects to the brainstem and spinal cord (but apparently not heavily to the striatum). As a whole, these caudally directed cortical outputs innervate primarily the motor and sensory systems as defined in Chapters 8 and 11, respectively (see also Fig. 7.5 in Chapter 7).

It should come as no surprise that the organization of caudally directed cortical connections, which provide the cognitive influence on behavior, are extensive and exceedingly complex. This is a topic that is far beyond the scope of the present discussion (for more on this topic, see the Selected Readings at the end of the chapter). However, it is important to appreciate that all of these cortical outputs are topographically organized, based fundamentally on the regional map indicated in Figures **10.4** and **10.5**. That is one reason why the importance of understanding the principles of cortical regionalization cannot be overemphasized. For example, virtually the entire cerebral cortex shares bidirectional connections with the thalamus, and it also sends a topographically organized axonal output to the striatum.

The corticostriatal projection leads us to consider the other half of the cerebral hemisphere: the cerebral (basal) nuclei.

The Cerebral Nuclei

As we saw earlier (Fig. **10.1**), the cerebral cortex and the cerebral (basal) nuclei are completely distinct structures in the endbrain vesicle of the very young embryo. However, because cerebral nuclei undergo relatively much more growth than cerebral cortex, they bulge inward and come to lie adjacent to parts of the cortex in the maturing (Fig. **10.9**) and adult (Fig. **10.10**) brain. There is a great deal of confusion and disagreement about exactly what constitutes the cerebral nuclei, and in fact about how to group the various components of the cerebral hemispheres (cerebrum). In dealing with the hemispheres, one encounters a bewildering assortment of terms, including limbic system, septum, amygdala, extended amygdala, rhinencephalon, corpus striatum, dorsal and ventral striatum and pallidum, neocortex, and so on.

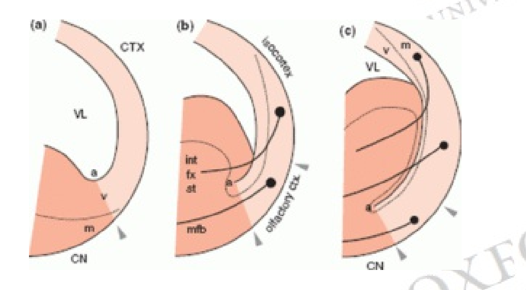


Figure 10.9
The differential growth of the cerebral nuclei (CN, darker red) as compared to the cerebral cortex (CTX, lighter red) during cerebral hemisphere embryogenesis is shown in these schematic drawings (from early, *a*, to later, *c*). Only the lateral part of the lateral (striatal) ventricular ridge is shown. Key: a, ventral angle of lateral ventricle; fx, fornix; int, internal capsule; m, mantle layer of neural tube; mfb, medial forebrain bundle; st, stria terminalis; v, ventricular layer of neural tube; VL, lateral ventricle. Adapted with permission from L.W. Swanson and G.D. Petrovich, What is the amygdala? *Trends Neurosci*., 1998, vol. 28, p. 325.

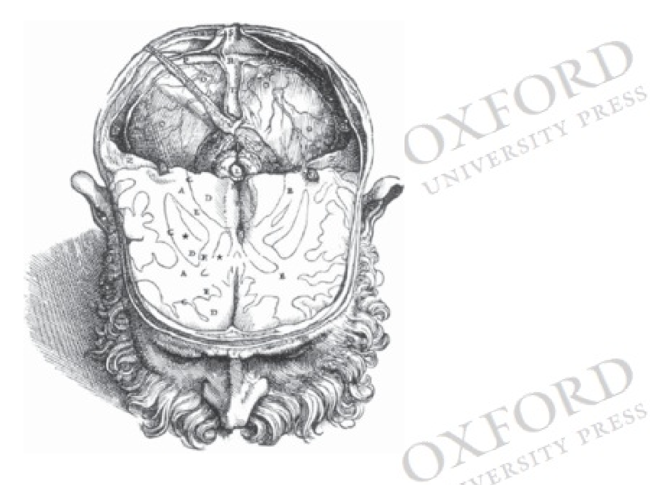


Figure 10.10
This drawing of the partly dissected head and brain is from Vesalius's *Fabrica* (1543). The caudal halves of the cerebral hemispheres were removed to reveal the pineal gland (L), tectum (M, N), and cerebellum. A transverse slice through the remaining cerebral hemispheres clearly reveals the pattern of gray and white matter. Note that on the left-hand side (the right hemisphere) the cerebral nuclei (basal ganglia) are clearly outlined (indicated by two asterisks, which have been added). It is one of a magnificent series of 15 drawings that illustrate a complete dissection of the brain. Compare with Figure 7.1, which, Vesalius wrote, he used in school to learn about the brain.

As mentioned earlier in the chapter, one way around this miasma is to adopt the view that the cerebral hemispheres consist simply of cortex and nuclei, with the *cerebral nuclei divided in two: striatum and pallidum*. If one simply begins with the regional map of cerebral cortex and considers the function and connections of its various areas, many of the terms just listed can seem unnecessary or even arbitrary and confusing.

This simple view of cerebral hemisphere regionalization is supported by embryology, by the fast-acting neurotransmitters used in extrinsic output connections from the cortex and nuclei, and as we shall see in the next section, by the organization of connections from cerebrum to motor system. What are the components of the cerebral nuclei, and how are they distributed between striatum and pallidum? Starting with embryology, differentiation of the young endbrain indicates that after the corticostriatal sulcus separates cerebral cortex from cerebral nuclei, the next feature to appear is the *striatopallidal sulcus* (Fig. **10.1**). It divides the presumptive cerebral nuclei into two longitudinal bulges called the lateral or dorsal (striatal) and medial or ventral (pallidal) ridges that are less differentiated at the rostral and caudal ends (Figs. **10.1** and **10.2**).

In addition to these topological features dictated by embryology (Figs. **10.1**, **10.2**, and **10.9**), it now seems clear that adult pyramidal cells, which generate the cortical axonal output, typically use the excitatory neurotransmitter glutamate, whereas the caudally directed axonal outputs of the cerebral nuclei typically use the inhibitory neurotransmitter GABA. Thus, if it is unclear whether a particular adult gray matter region in the cerebral hemisphere is part of cortex or nuclei, the major neurotransmitter used in its caudally

directed output is one criterion for helping to decide. The cerebral cortex also contains a large population of GABAergic neurons. However, they are intraregional interneurons rather than interregional neurons, and John Rubenstein and others have demonstrated that most if not all of them are actually born in the cerebral nuclei region of the early embryo, and then migrate tangentially—dorsally—into the developing cerebral cortex. Thus, most if not all cerebral GABAergic neurons may be generated in the embryonic nuclear or basal region and then migrate to cortex in a direction opposite that of caudally directed cortical axonal outputs (Fig. **10.9**b,c).

Based on these embryological and neurotransmitter utilization criteria, we can assign all noncortical cerebral gray matter regions to the cerebral nuclei, and like the cerebral cortex they are arranged in a topographically ordered way (Fig. **10.11**). Further assignment to either the striatal or pallidal division of the cerebral nuclei may be done tentatively on the basis of known embryological relationships, and by analogy to the connectional model of the classic striatum (caudate nucleus and putamen) and pallidum (globus pallidus), which we will now review.

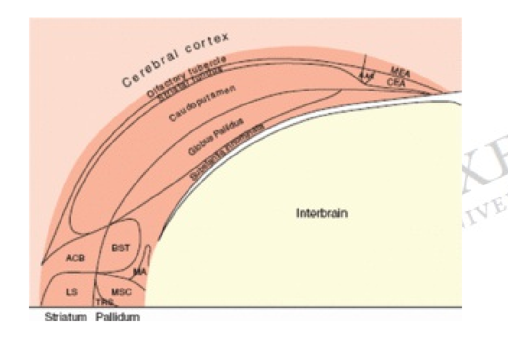




Figure 10.11
The overall arrangement of cell groups (gray matter regions) within the cerebral nuclei (telencephalic basal ganglia) viewed on a flatmap of the rat brain. Note that the cerebral nuclei may simply be divided into striatal (STR) and pallidal (PAL) domains. Key: AAA, anterior amygdalar nucleus; ACB, nucleus accumbens; BST, bed nuclei of stria terminalis; CEA, central amygdalar nucleus; LS, lateral septal complex; MA, magnocellular (preoptic) nucleus; MEA, medial amygdalar nucleus; MSC, medial septal complex; TRS, triangular septal nucleus. Adapted with permission from L.W. Swanson, *Brain Maps: Structure of the Rat Brain*, third edition (Elsevier: Amsterdam, 2004, plate opposite p. 14).

Triple Caudal (Descending) Projection from Cerebrum

Is there a basic elementary network architecture that all or most parts of the cerebral hemispheres participate in? One appealing possibility involves its caudally directed axonal output to the motor system (Fig. **10.12**). It did not become clear until the 1960s that the entire isocortex generates a topographically organized projection to the entire dorsal striatum (the caudate and putamen, caudoputamen; see later discussion). It is now known that this projection arises predominantly from layer 5 pyramidal neurons that use the typically excitatory neurotransmitter glutamate. It is also known that this striatal input is generated by collaterals of axon trunks that extend caudally at least as far as the brainstem. Thus, a population of layer 5 cortical neurons provides simultaneous excitatory inputs to the dorsal striatum as well as to the motor system broadly defined (see Chapter 8).

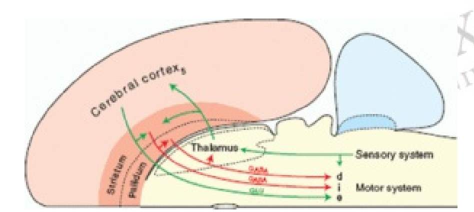


Figure 10.12
General organization of a triple caudally directed (descending) projection from the cerebral hemispheres (cognitive system) to the motor system broadly defined. Note that there are also thalamocortical and thalamostriatal feedback loops, and that most, but not all sensory systems project to the thalamus that in turn projects to the cerebral cortex. In the isocortex, most caudally directed projections arise from layer 5 pyramidal neurons as indicated. Key: Green arrows use glutamate (GLU) as an excitatory neurotransmitter; red arrows use GABA as an inhibitory neurotransmitter; d, disinhibitory; e, excitatory; i, inhibitory. Adapted with permission from L.W. Swanson, Anatomy of the soul as reflected in the cerebral hemispheres: neural circuits underlying voluntary control of basic motivated behaviors, *J. Comp. Neur.*, 2005, vol. 493, p. 124.

The second part of the elementary cerebral network to the motor system involves the caudally directed axonal connections of the dorsal striatum, which utilize the typically inhibitory neurotransmitter GABA. This projection is relatively quite simple. The caudate and putamen together provide a topographically organized projection to the entire globus pallidus (both external and internal parts, called the dorsal pallidum; see later discussion), and to the entire substantia nigra (both reticular and compact parts). It has now been established by André Parent and others that the dorsal striatal projection to the dorsal pallidum generally arises as collaterals of axon trunks that go on to terminate in the substantia nigra. Thus, individual neurons in the dorsal striatum typically provide a dual inhibitory input to the dorsal pallidum and substantia nigra. Recall that the reticular substantia nigra is part of the behavior control column, concerned in part with generating orienting movements of the eyes and head (see Chapter 8, Fig. 8.11).

The third and final part of the elementary cerebral network to the motor system involves the caudally directed axonal output of the dorsal pallidum. As with the dorsal striatum, they use GABA as a neurotransmitter, and they too generate a branched axonal output, this time to the motor system broadly defined as well as to the dorsal thalamus. Because the dorsal pallidum receives an inhibitory input from the dorsal striatum, the caudally directed pallidal output to the motor system can be thought of as *disinhibitory* (an inhibitory projection is inhibited), a term introduced by Eugene Roberts, who discovered GABA in the nervous system. For example, both the dorsal striatum and the dorsal pallidum project heavily to the reticular part of the substantia nigra, as do certain areas of the cerebral cortex (motor-related areas of the frontal region). It seems likely that the direct cortical input is excitatory, the striatal input is inhibitory, and the pallidal input is disinhibitory (Fig. **10.12**).

The elementary cerebral network under discussion so far has two essential components—a triple cascading projection (connection) to the motor system broadly defined, and a thalamocortical feedback loop. Thus, cortical neural activity (which at least partly represents cognition) has a direct influence on the motor system, and it is also fed back upon the cortex to influence subsequent neural activity there. Furthermore, it is now clear that, taken as a whole, the dorsal thalamus generates a topographically organized axonal output to the entire dorsal striatum (Fig. **10.12**). Thus, the dorsal thalamus actually provides an ordered axonal input to the whole isocortex and to the whole dorsal striatum—which we have seen in turn receives an ordered input from the whole isocortex.

The next critical step in the analysis is this. Does this elementary cerebral network apply just to isocortex, caudoputamen, and globus pallidus—or is it characteristic of most or all of the cerebral hemisphere? Our analysis of the connectional data now at hand suggests that the latter is the case.

The first real breakthrough in this line of thinking was provided in 1975 by Lennart Heimer and R.D. Wilson. With brilliant insight, they suggested that there is a ventral striatum and ventral pallidum, which would complement the “classical” dorsal striatum (caudate and putamen) and dorsal pallidum (globus pallidus). The ventral striatum consisted primarily of the nucleus accumbens and olfactory tubercle, which project to the ventral pallidum (in the substantia innominata), and the latter in turn projects to the thalamus. Thus, both the dorsal and ventral striatopallidum form a thalamocortical loop, although the projections are topographically organized so that different parts of the thalamus and cortex are influenced by the dorsal and ventral cerebral nuclei.

We then extended this view to include all of the cerebral nuclei, and virtually the entire cerebral cortical mantle. The suggested arrangement of cerebral nuclei is outlined in Figure **10.13**, and the basic hypothesis is that all regions of the cerebral nuclei are derived embryologically from either the lateral-dorsal (striatal) ventricular ridge or the medial-ventral (pallidal) ventricular ridge (see Figs. **10.1** and **10.2**).

Cerebral nuclei	*Dorsal*	*Ventral*	*Medial*	*Caudorostral*
STRIATUM	CP	ACB FS OT	LSC	MEA CEA AAA IA
PALLIDUM	GPe GPi	SI MA	MSC	BST

Figure 10.13
General topographic organization of gray matter regions in the mammalian cerebral nuclei (striatum and pallidum); also see Figures **10.1**, **10.5**, and **10.11**. Key: AAA, anterior amygdalar area; ACB, nucleus accumbens; BST, bed nuclei stria terminalis; CEA, central amygdalar nucleus; CP, caudoputamen; FS, funds of striatum; GPe,i, globus pallidus external, internal parts; LSC, lateral septal complex; MA, magnocellular (preoptic) nucleus; MEA, medial amygdalar nucleus; MSC, medial septal complex; OT, olfactory tubercle; SI, substantia innominata. Adapted with permission from L.W. Swanson, Cerebral hemisphere regulation of motivated behavior, *Brain Res*., 2000, vol. 886, p. 133.

There appear to be two new features in this scheme: the addition of medial and caudorostral divisions of the striatopallidum or cerebral nuclei. In this scheme, the lateral septal complex is striatum for hippocampal cortex or Ammon's horn, a suggestion first made by Cajal over a century ago, and the medial septal complex is the pallidum associated with hippocampus and lateral septal complex. Furthermore, certain regions of the traditional amygdala that have GABAergic output neurons—in particular the central and medial nuclei—are regarded as striatum for certain areas of olfactory and visceral cortex, and the bed nuclei of the stria terminalis are regarded as the corresponding pallidum. These arrangements fit the overall scheme because both supposed pallidal components (medial septal complex and bed nuclei of the stria terminalis) establish thalamocortical feedback loops, and both are derived from the embryonic medial ventricular ridge.

From the standpoints of embryology and adult connections, the cerebral hemispheres appear to form an integrated unit—which from the functional perspective is responsible for elaborating cognition and for transmitting cognitive influences to the motor, sensory, and behavioral state systems. The key to understanding the cerebral hemispheres lies in the arrangement of the structure–function regionalization map of the cerebral cortex. The thalamus connects in a topographically ordered way to virtually all of the cerebral cortex, and almost all of it in turn connects in a topographic way to the cerebral nuclei. Superficial (supragranular) pyramidal cells establish an immensely complex network of connections between the various cortical areas in the hemispheres on both sides of the brain, and this network must play a critical role in elaborating various aspects of cognition. Deep (infragranular) pyramidal neurons receive inputs from superficial pyramidal neurons and send massive caudally directed axonal outputs to the cerebral nuclei, brainstem, and spinal cord. That is, deep pyramidal neurons play a key role in transmitting the results of neural activity in the intracortical network to the motor, sensory, and behavioral state systems. We now turn to a consideration of how information about the external and internal environments enters the nervous system to influence the cognitive, motor, and behavioral state systems.

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Larry W. Swanson



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The Sensory System : Inputs from Environment and Body

Chapter: The Sensory System
Author(s): Larry W. Swanson
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> *"Impressions conveyed by the sensitive nerves to the central organs are either reflected by them upon the origin of the motor nerves, without giving rise to true sensations, or are conducted to the sensorium commune, the seat of consciousness."*
>
> Johannes Müller (1843)
>
> *"It is probable that there is in the brain a certain part or element appropriated to the affections, and the excitement of which causes every idea to acquire the intensity of emotion, and which, when very active, gives the simplest thought, even in dreams, the character of passion; but the existence of such a part or element cannot be strictly proved, nor its locality demonstrated."*
>
> Johannes Müller (1843)

In many ways the sensory system is the easiest for us to understand at an almost intuitive level. The eye has a lens like a camera, and a retina for capturing focused visual scenes almost like film or image sensor, and then those scenes are transmitted by the optic nerve to the brain where they are somehow converted into sensations and perceptions. And the same principle basically applies for sounds detected by the ear, odors detected by the nose, tastes detected by the tongue, hunger pangs detected by the stomach, and tickles and pinches detected by the skin.

Unavoidably, various aspects of the sensory system have already been dealt with in earlier chapters. We have seen that during the course of evolution various ectodermal cells became specialized to detect a wide range of stimuli from the external and internal environments. These receptor cells have been called *exteroceptors* and *interoceptors*, respectively (Fig. 7.5 parts 1 and 2, respectively, in Chapter 7). Examples of stimuli include chemicals (and the corresponding receptor cells, *chemoreceptors*), temperature (*thermoreceptors*), mechanical deformation (*mechanoreceptors*), light (*photoreceptors*), and osmolality (*osmoreceptors*). From a strictly introspective point of view, you are conscious of the fact that stimuli detected by the eye and ear produce two entirely different sensory modalities. Johannes Müller, quoted at the beginning of the chapter, ascribed this qualitative difference between the classic sensory modalities (touch, taste, smell, vision, and hearing) to "specific nerve energies"—because of them stimulation of a particular sense organ generates its own particular sensation and no other. Today, most neuroscientists have an alternative explanation. Each sensory system reaches a different region of cerebral cortex, where the qualitatively different conscious experiences associated with each sensory modality are elaborated (Figs. 10.5–10.7 in Chapter 10).

We have also seen earlier in the book that the sensory system projects to the motor and behavioral state systems, in addition to the cognitive system, where conscious awareness is elaborated (Chapter 7). Direct sensory inputs to the motor system produce reflex behaviors without conscious awareness. In this chapter we will look more carefully at certain general features that characterize the sensory system, as well as special features that distinguish between the various sensory modalities in mammals. No attempt will be made to describe in detail the fascinating architecture of the individual sensory organs or the detailed circuit organization of each of the sensory subsystems. The latter topics are covered nicely in any introductory neuroscience textbook. Unraveling the anatomy, physiology, and chemistry of the sensory systems was a crowning achievement of post–World War II neuroscience.

Evolution and Development of Sensory Neurons

We saw in Chapter 3 that bipolar sensory neurons probably first evolved in the outer body wall layer (the ectoderm, facing the external environment) of Cnidarians like hydra. In more complex invertebrate animals like worms that have a central nervous system, the axon from sensory neurons in the ectoderm extends into a ganglion of the ventral nerve cord. There the axon trunk typically bifurcates, sending one bifurcation branch rostrally and the other caudally—with each branch in turn issuing relatively short collaterals that ramify in the nearby neuropil (Figs. 4.2 and 4.4 [in Chapter 4] and 11.1A). In more advanced invertebrates, like mollusks for example (Fig. **11.1**B), the cell body of many sensory neurons migrates during development into the interior of the animal, just deep to the ectodermal epidermis. This arrangement provides a competitive advantage because the trophic center (the nucleus with its chromosomes, and most of the protein synthetic machinery) of the sensory neuron is better protected from potential damage inflicted by insults from the external environment. Note that here the bipolar sensory neuron's receptive pole or extension (the dendrite) becomes elongated.

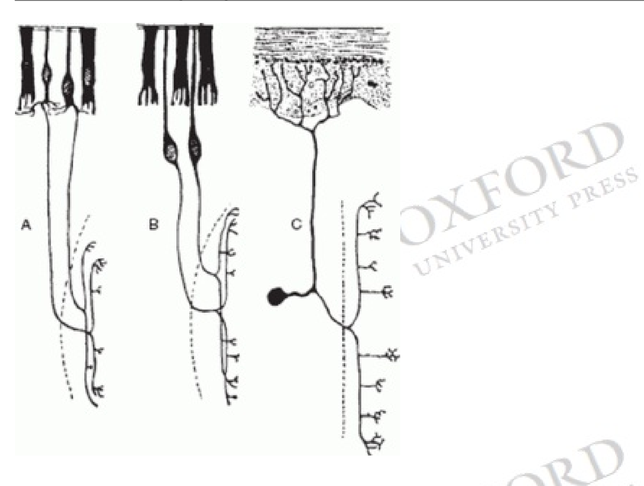




Figure 11.1
The progressive centralization of sensory neuron cell bodies in the earthworm (A), mollusk (B), and typical vertebrate. Golgi method. From S.R. Cajal, *Histologie du système nerveux de l'homme et des vertébrés*, vol. 1 (Maloine: Paris, 1909, p. 11), based on the work of Retzius.

Turning now to vertebrates we find that typically, sensory neurons innervating the skin have a cell body that is located in a spinal or cranial nerve ganglion deep within the body. In fact, these ganglia are very protected from injury. So much so that they lie within a pocket formed by the vertebrae themselves or by the skull. However, it is very interesting to see that in the adult, they do not have a bipolar shape. Instead, they have a rounded cell body with a single extension that forms a Y-shaped arrangement (Figs. 7.4 [in Chapter 7] and 11.1C). This single extension is the dendrite, and it courses peripherally through a mixed nerve toward the periphery or the viscera. The central, thinner part of the Y-shaped arrangement is the axon, and it extends through a dorsal root into the spinal cord, or through certain cranial nerves to the brainstem. These spinal and cranial nerve ganglion neurons have what is called a *pseudounipolar* shape, because as we shall now see they develop from a typical bipolar shape in the embryo.

Toward the end of the nineteenth century Wilhelm His discovered that bird and mammalian spinal nerve ganglion neurons start out in the early embryo as polygonal or multipolar cells with short extensions. They then progress to a simpler bipolar stage with a thick extension growing toward the periphery and a thin extension growing toward the central nervous system (Fig. **11.2**A). Finally, the nucleus of each cell begins to migrate at right angles to the dual extensions, toward the periphery of the ganglion (Fig. **11.2**C then B). This migration of the nucleus, along with the accompanying perikaryon, produces the definitive, adult pseudounipolar shape of spinal and cranial nerve ganglion neurons. The stem of the Y is thick and extends uninterrupted to the periphery or viscera. Functionally it is the dendrite because it detects stimuli and conducts them toward the axon, which arises from the sharp bend of the dendrite within the ganglion. The axon is thinner than the dendrite and conducts information into the central nervous system. In vertebrates, it is quite common for the axon of a neuron to arise from a dendrite. For example, this arrangement is found in neuron types as varied as cerebral cortical pyramidal neurons and cerebellar cortical granule cells.

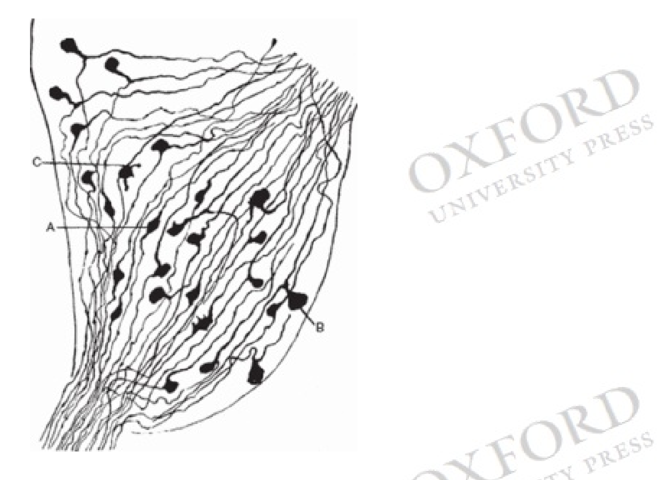




Figure 11.2
The appearance of developing spinal nerve ganglion neurons in an approximately 9-week-old human embryo. All stages from bipolar (A) to pseudounipolar (B) can be seen in this drawing of Golgi-stained material. From S.R. Cajal, *Histologie du système nerveux de l'homme et des vertébrés*, vol. 1 (Maloine: Paris, 1909, p. 643).

For the sake of completeness, recall (see Chapter 5, section on "Neural Crest and Placodes") that not all "spinal nerve ganglion cells" are found in spinal nerve ganglia. In 1877 Freud discovered that in lampreys (a primitive vertebrate) some of these sensory neurons are found in ganglia near the spinal cord, and some are actually found within the spinal cord itself. Then a few years later Retzius discovered that in a protovertebrate, amphioxus, most of the sensory neurons are found within the spinal cord—and many are bipolar in the adult. All of these sensory neurons are derived from the embryonic ectoderm, of course, but in the more advanced vertebrates the neural crest and epibranchial placodes are more clearly differentiated from the neural plate that goes on to generate the neural tube and thus spinal cord.

Overview of Sensory Neurons

Most sensory neurons in humans and other mammals are variations on the bipolar and pseudounipolar ganglion cells just discussed (see Fig. **11.3**). Olfactory neurons are the closest to the primitive bipolar sensory neurons found in earthworms, for example (Figs. 4.4 [in Chapter 4] and 11.1A). The cell bodies of olfactory neurons lie in the olfactory mucosa of the nose (Fig. **11.3**A, B)—that is, in a specialized epithelial cell layer derived from the ectoderm. Their axon extends all the way to the brain, where they synapse with the dendrites of mitral cells in the olfactory bulb of the cerebral cortex (see later discussion).

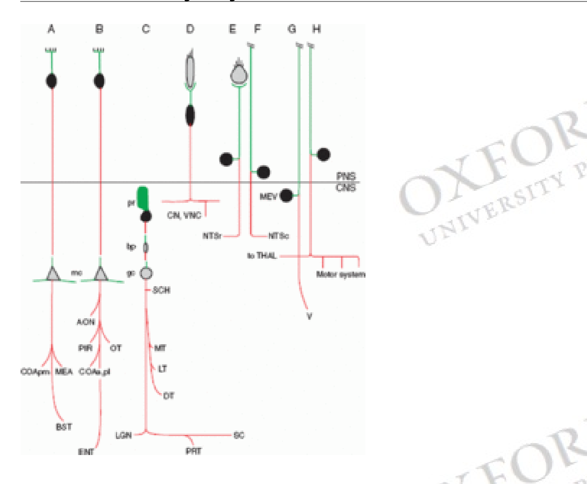




Figure 11.3
The basic arrangement of the various sensory neurons (black cell bodies with green dendrites and red axons) found in mammals. Certain secondary neurons (gray cell bodies) are also shown for clarity. Key: A, vomeronasal neurons; B, olfactory mucosa neurons; C, photoreceptors; D, spiral and vestibular ganglion cells receiving information from hair cells; E, geniculate, glossopharyngeal, and vagal ganglion cells receiving information from taste receptors; F, glossopharyngeal and vagal ganglion cells innervating the viscera; G, midbrain nucleus of the trigeminal nerve; H, spinal nerve ganglion cells. AON, anterior olfactory nucleus (area); bp, retinal bipolar cell; BST, bed nuclei stria terminalis; CN, cochlear nuclei; CNS, central nervous system; COAa, pl, pm, cortical amygdalar nucleus, anterior, posterolateral, posteromedial parts; DT, dorsal terminal nucleus, accessory optic tract; ENT, entorhinal area; gc, retinal ganglion cell; LGN, dorsal lateral geniculate nucleus; LT, lateral terminal nucleus; mc, mitral cell; MEA, medial amygdalar nucleus; MEV, midbrain nucleus of trigeminal nerve; MTN, medial terminal nucleus; NTSc, r, nucleus of solitary tract, caudal, rostral parts; OT, olfactory tubercle; PIR, piriform area; PNS, peripheral nervous system; pr, photoreceptor; PRT, pretectal region; SC, superior colliculus; SCH, suprachiasmatic nucleus; THAL, thalamus; V, motor nucleus of trigeminal; VNC, vestibular nuclei.

In contrast, bipolar sensory neurons whose cell body has migrated deeper into the body as in mollusks (Fig. **11.1**B) are represented in the auditory and vestibular systems, which utilize the vestibulocochlear or eighth cranial nerve (Fig. **11.3**D). Bipolar neurons whose dendrites extend to the organ of Corti in the cochlea are concentrated in the spiral ganglion, and their axons end in the cochlear nuclei of the brainstem. Bipolar neurons whose dendrites extend to the semicircular canals, saccule, and utricle (the other half of the inner ear) are concentrated in the vestibular ganglion, and their axons end in the vestibular nuclei of the brainstem. Interestingly, the dendrites (and sometimes even the cell bodies) of eighth nerve bipolar neurons are myelinated and conduct action potentials.

Stimuli associated with hearing and equilibrium are detected by sensory cells called *hair cells* in the organ of Corti, and in the saccule, utricle, and semicircular canals, respectively. Hair cells are mechanoreceptors whose “hairs” (actually microvilli and cilia) detect pressure changes in the fluid surrounding them. Although they are sensory cells, hair cells are not traditionally regarded as neurons. They are derived from nonneural epithelium lining the cavity of the inner ear (a lining called the membranous labyrinth). Taste cells (Fig. **11.3**E) are another example of nonneural sensory cells that are generated from a specialized epithelium, in this case associated with the tongue and nearby tissues.

Pseudounipolar sensory neurons are very common in mammals (Figs. **11.1**C and **11.3**E–H). The prototype (Fig. **11.3**H) is the spinal nerve ganglion cell, which is associated with each spinal nerve (Figs. 7.4 [in Chapter 7] and 8.4 [in Chapter 8]), along with the fifth cranial nerve trigeminal ganglion cell, which is analogous to a spinal nerve ganglion cell for the skin of the head. The fact that the axon of spinal nerve ganglion neurons bifurcates into rostrally and caudally directed branches on entering the spinal cord was discovered and described in 1885 by the great Norwegian scientist, arctic explorer, politician, and philanthropist Fridtjof Nansen (1861–1930), who won the Nobel Peace Prize in 1922. It was part of his thesis work on the lowly hagfish (*Myxine glutinosa*) at the Bergen Museum. Soon thereafter Cajal went on to show that this bifurcation is also universally true in birds and mammals, and that the bifurcation branches in turn generate abundant collaterals that end in the spinal gray matter. Thus, the terminals of a spinal nerve ganglion cell can contact a large number of postsynaptic neurons, including motor neurons, interneurons associated with central pattern generators, and neurons with rostrally directed connections to various parts of the brainstem, including the thalamo-cortical projection system (Fig. 7.4 in Chapter 7). There is very extensive divergence of information transmission at the first stage of the spinal nerve/trigeminal ganglion sensory system.

There are other variations on the pseudounipolar sensory neuron theme. One example involves neurons in the ganglia of the ninth (glossopharyngeal) and tenth (vagus) cranial nerves (Fig. **11.3**F). They detect a wide range of sensory information from the viscera (and very limited amounts from soma) and transmit this information to the caudal end of a hindbrain sensory nucleus, the *nucleus of the solitary tract* (for somatic information, the adjacent trigeminal nucleus). Unlike the axon of spinal nerve ganglion cells, the axon of these vagal and glossopharyngeal ganglion cells typically does not bifurcate. Instead, it enters the brainstem and extends caudally through the solitary tract, where it branches to innervate the nucleus associated with the tract. Another example involves the pseudounipolar sensory neurons that innervate taste buds (Fig. **11.3**E). These neurons are found in three ganglia (the distal ganglia of the ninth and tenth cranial nerves, and the geniculate ganglion of the intermediate part of the seventh cranial nerve). Their axon courses rostrally in the solitary tract to innervate the rostral end of the tract's nucleus, which is specialized for gustation as opposed to viscerosensation. The final example involves the midbrain nucleus of the trigeminal nerve, which is a “spinal nerve ganglion” in the brain, on the edge of the midbrain periaqueductal gray matter (Fig. **11.3**G). It forms the input side of stretch reflexes that help control the muscles of mastication (chewing), which are innervated by the motor nucleus of the trigeminal (fifth cranial) nerve.

The last type of sensory neuron we come to is the *photoreceptor* of the eye (Fig. **11.3**C). Curiously, perhaps, the retina, which contains a monolayer sheet of photoreceptors, is an outgrowth of the brain—of the hypothalamus in fact (Chapter 6). Thus, photoreceptors are central nervous system neurons. Their axon synapses with or innervates the dendrites of retinal bipolar cells (intraregional interneurons), whose axon in turn synapses with retinal ganglion cells, which are the output neurons that form the optic nerves, chiasm, and tracts transmitting the results of retinal visual information processing to the rest of the brain (Fig. 6.6 in Chapter 6). Photoreceptors are incredibly sensitive. Apparently they can detect and thus respond to a single photon.

Overview of Sensory Pathways

The basic plan of the nervous system outlined in this book stresses the fact that the sensory system as a whole projects to the motor system, to the behavioral state system, and to the cognitive or cerebral system (see Fig. 7.5 in Chapter 7). Exactly how this is accomplished for each particular sensory modality is beyond our scope here. Instead we will outline the major features of each modality in the following sections. From this perspective it appears safe to conclude that there are few if any generalizations that apply to all of the various sensory modalities. In fact, attempts to formulate such generalizations or principles in textbooks have led to needless confusion and misconceptions. For example, not all sensory information reaches the cerebral cortex by way of a “relay” in the thalamus. Instead, olfactory sensory neurons project directly to the cerebral cortex (the olfactory bulb)—and visceral sensory information from the nucleus of the solitary tract can reach the cortex directly, as well as by way of a relay in the thalamus. Information from each sensory modality reaches the cerebral cortex in a different way (Fig. **11.4**).

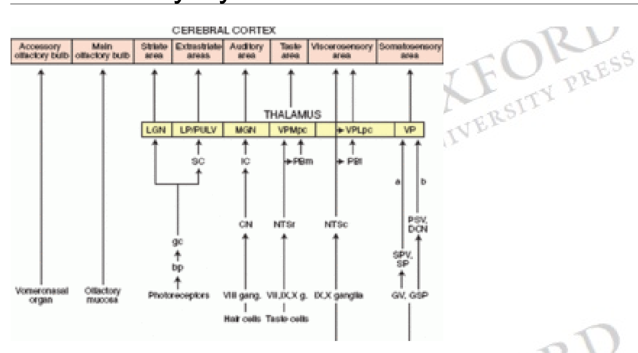




Figure 11.4
Schematic outline of routes for different classes of sensory information to reach the cerebral cortex (light red), much but not all by way of the thalamus (yellow). Key: a, b, spinothalamic tract and medial lemniscus, respectively; bp, retinal bipolar cell; CN, cochlear nuclei; DCN, dorsal column nuclei; gc, retinal ganglion cell; GSP, spinal nerve ganglion; IC, inferior colliculus; GV, trigeminal ganglion; LGN, dorsal lateral geniculate nucleus; LP/PULV, lateral posterior nucleus/pulvinar; MGN, medial geniculate nucleus; NTSc, r, nucleus of solitary tract, caudal, rostral parts; PBl, m, parabrachial nucleus, lateral, medial divisions; PSV, principal trigeminal sensory nucleus; SC, superior colliculus; SP, spinal cord; SPV, spinal trigeminal nucleus; VP, ventral posterior nucleus; VPLpc, ventral posterolateral nucleus, parvicellular part; VPMpc, ventral posteromedial nucleus, parvicellular part.

We have seen in Chapter 8 that the motor system core (excluding the cerebellum) may be analyzed effectively in terms of a hierarchical organization scheme. The sensory system is different. For a considerable distance, each of the pathways associated with various sensory modality classes remains separate. That is, they are arranged in parallel, at least in terms of the primary modality classes (vision, audition, olfaction, taste, and somatovisceral). Convergence takes place in polymodal regions of the cerebral hemispheres, and in specialized regions of the brainstem—most (if not all) of which are parts of the behavioral state and motor systems.

Forebrain Sensory Systems: Olfactory, Visual, Humoral, and Osmotic

The forebrain is the most complex part of the nervous system, and it has a number of special sensory systems that are quite unique and play an important role in generating this level of complexity. The extent to which these sensory systems are differentiated relative to one another (their relative size in crude terms) varies greatly among species. For example, the olfactory sense is very prominent in mice, and relatively paltry in humans—whereas the reverse is true for the visual system. Humans have a relatively elaborate visual system as compared to nocturnal, almost blind mice that tend to avoid light whenever possible. The olfactory and optic nerves are the major cranial nerves of the forebrain. Their relative sizes vary greatly between humans and mice, and yet both sensory systems have the same basic organization, the same fundamental plan—not only in both species but also in all mammals. This is simply a variation on a theme emphasized in each chapter: there is a basic plan of the mammalian nervous system, and the nervous system in each species is a quantitative variation on that theme.

Let's begin with the first cranial nerve, the olfactory nerve. As we have already seen, it has very primitive—or perhaps more accurately, very ancient and thus very conserved—features, and it is in many ways the simplest of the sensory systems in terms of network organization (see Fig. **11.4**). However, before we get to the main olfactory system, it is important to realize that the traditional classification of 12 cranial nerves (see Chapter 8, section on “Distribution of Somatic Motor Neuron Pools”) breaks down completely here because there are at least three nerves associated with the rostral end of the central nervous system.

Although the *olfactory nerve* is cranial nerve I, there is also a distinct *vomeronasal nerve* that is unnumbered. It arises from a pit in the olfactory mucosa where the bipolar sensory neurons are specialized to detect pheromones—molecules released into the air by one animal and detected by another animal, to influence various aspects of social behavior (for example, sexual, parental, and territorial behaviors). The vomeronasal nerve provides a beautiful example of major differences between species. The vomeronasal system is very prominent in rodents, where it is essential for reproductive behaviors, but is absent in the vast majority of adult humans. However, this absence in the adult human is the result of atrophy. It does not reflect a fundamental difference in terms of a complete absence in one species. The vomeronasal system develops in the human embryo just as it does in rodents, but later on it degenerates (for unknown reasons).

In addition, there is an enigmatic *terminal nerve* that was discovered in the second half of the nineteenth century, and it also does not have a number in the 12 cranial nerve scheme. It appears to innervate the nasal mucosa and send axons into the brain in the region of the terminal lamina; that is, in the medial septal-diagonal band complex of the cerebral nuclei and the adjacent preoptic region of the hypothalamus. Recently, the terminal nerve has attracted attention because it probably forms the route taken by GnRH neuroendocrine neurons (which control the reproductive cycle) migrating from their embryonic birthplace in the olfactory epithelium to their final resting place in the basal forebrain (see Chapter 8, section on “The Neuroendocrine Motor System”).

The initial stages of the vomeronasal system are very simple indeed. The vomeronasal nerve ends in the *accessory olfactory bulb*, a specialization of the *main olfactory bulb* where the olfactory nerve ends in the brain. Topologically and embryologically, the main and accessory olfactory bulbs are the earliest differentiations of the cerebral cortex (Fig. 10.5 in Chapter 10), and various authorities, including Cajal and Brodmann, have thought with good reason that these two parts of the bulb are primary sensory cortices for the main and accessory olfactory systems, respectively. In other words, the vomeronasal nerve ends entirely and thus exclusively in the primary vomeronasal cortex—the accessory olfactory bulb (Figs. **11.3** and **11.4**).

Fortunately, the projections of the primary vomeronasal cortical area are very simple and follow the most basic projection pattern of other unimodal sensory areas (Fig. 10.12 in Chapter 10). The accessory olfactory bulb projects massively to an *association vomeronasal cortical area* (the posteromedial cortical amygdalar nucleus) and a *region of the striatum* (the medial amygdalar nucleus; Fig. 10.11 in Chapter 10). To complete the picture, the accessory bulb projects lightly to a *region of the pallidum* (the principal nucleus of the bed nuclei of the stria terminalis, which receives a massive input from the striatal component, the medial amygdalar nucleus). Thus, the accessory olfactory system participates in a classic triple caudally directed or descending projection to the motor system (Fig. 10.12 in Chapter 10) from cerebral cortex, striatum, and pallidum. Its major inputs to the motor system involve the hypothalamus, and in particular the rostral group of medial nuclei that control the expression of social behaviors, and the visceromotor pattern generator network next to it in the periventricular region (Fig. 8.11 in Chapter 8).

The main olfactory system is more complex because its primary sensory cortical area (the main olfactory bulb) has much more widespread projections to secondary olfactory cortical areas. They include, among others, the anterior olfactory nucleus (area), piriform area, anterior and posterolateral parts of the cortical amygdalar nucleus, and entorhinal area of the hippocampal formation (Fig. **11.3**). The striatal projection of primary olfactory cortex (main olfactory bulb) is primarily to the olfactory tubercle, which lies just rostral to the accessory olfactory striatum (the medial amygdalar nucleus), and the corresponding region of pallidum is centered in restricted (rostroventral) parts of the substantia innominata (ventral pallidum). The secondary main and accessory olfactory cortical areas are not strictly unimodal. They receive information from each other, and thus to some extent, at least, integrate information from both differentiations of the olfactory system. The primary main olfactory cortical area does not project to the brainstem. Instead, the secondary main olfactory cortical areas (especially those in the amygdalar region) and the substantia innominata carry olfactory information to the brainstem, mainly to the hypothalamus, and restricted parts of the thalamus.

There is an enormous literature on the visual system, and we can only touch on selected highlights here. To start with, the processing of visual information in the retina is

exceptionally complex. It is well known that bipolar neurons "relay" information from photoreceptors to retinal ganglion cells, which in turn send this information through the optic nerves, chiasm, and tracts to the rest of the brain (Fig. **11.3**). In addition, there are two layers of other intraregional interneurons (horizontal and amacrine cells), and they spread information from photoreceptors tangentially through the retina. Thus, there are five basic neuron classes in the retina, and the actual details of information processing within the network that they form are vaguely understood.

One reason for this lack of understanding is the extensive differentiation of each of the five retinal neuron classes into groups, types, and varieties with important functional differences. For example, there are two groups of photoreceptors, rods and cones, which are responsible for night and day (color) vision, respectively. In addition, there are in many species three types of cones that are maximally sensitive to red, green, and blue wavelengths of light. Finally, there are at least three major groups of bipolar cell, at least three major types of ganglion cell, and dozens of varieties of horizontal and amacrine cells.

The *optic nerve* terminates quite extensively in the brain. Its first offshoot is to the suprachiasmatic nucleus, which lies just dorsal to the *optic chiasm* (where the optic nerves from each eye cross or partly cross to the other side of the brain), and it is the brain's primary circadian rhythm generator or clock (see Chapter 9, section on "Circadian Rhythms"; Fig. **11.3**). Just beyond this level an offshoot of the *optic tract* (the name for the continuation of the optic nerve beyond the chiasm), the *accessory optic tract*, splits off and courses to the midbrain, where it ends in three terminal nuclei (medial, lateral, and dorsal). They play an important role in controlling eye movements and are thus parts of the motor system. The main optic tract continues on to end in the superior colliculus or optic tectum of the midbrain, after giving off collaterals to the lateral geniculate complex of the thalamus and to the pretectal region (Fig. **11.3**). The dorsal part of the lateral geniculate nucleus then projects to primary visual cortex (Fig. 10.6 in Chapter 10), whereas the pretectal region is involved in visual reflexes, and the superior colliculus has two main roles: projecting to the motor system, and projecting to secondary visual cortical areas via the thalamus (Fig. **11.4**). Other less prominent, and less understood, terminal fields of the optic nerve in mammals include the lateral hypothalamic area, anterior thalamic nuclei, bed nuclei of the stria terminalis, and dorsal raphé nucleus.

The subfornical organ is an embryonic differentiation of the forebrain roof plate, in a dorsal region at the junction between interbrain (thalamus) and endbrain. This nucleus lacks the normal blood–brain barrier so that its neurons are exposed directly to peptide hormones in the blood. One such hormone is angiotensin II, whose levels go up when there is a loss of body fluid because of dehydration or hemorrhage. Under these conditions mechanisms operate to maintain blood pressure and to initiate drinking behavior that replenishes lost supplies of body water. Neurons in the subfornical organ have angiotensin II receptors, and when they are activated three subfornical outputs to other parts of the brain are presumably activated. One axonal output modulates hypothalamic inputs to medullary autonomic baroreceptor reflex centers that control blood pressure, another output modulates the release of hypothalamic neuroendocrine hormones that regulate body water retention and blood pressure, and yet another pathway stimulates thirst and drinking behavior. Thus, the subfornical organ is a "humerosensory" organ or nucleus that detects hormone levels in the blood. Like the retina, its sensory neurons are derived from the brain.

Next we come to the osmoreceptors of the hypothalamus. It has been known since the classic studies of Earnest Basil Verney and Bengt Andersson starting in the 1940s that they are found in the rostral end of the hypothalamus, around the rostral end of the third ventricle; and that they are responsible for eliciting drinking and the secretion of hypothalamic neuroendocrine hormones regulating body water. Their precise cellular identity remains a mystery, but it is clear that they respond to increased osmolality (or possibly sodium concentration) of the blood due to loss of body water. There is good reason to believe that the subfornical organ sends an axonal output to these preoptic region osmoreceptors, so that the subfornical organ angiotensin-sensing neurons and the preoptic osmosensitive neurons work together as part of a system controlling drinking behavior and body water regulation.

Finally, there are multiple neuron populations in the arcuate nucleus of the hypothalamus that play a role in regulating eating behavior by detecting and responding to a number of circulating hormones, including insulin from the pancreas, leptin from white fatty tissue, and ghrelin from the stomach. The subfornical organ, hypothalamic osmoreceptors, and arcuate nucleus play complementary roles in regulating hypothalamic control mechanisms for eating and drinking behaviors (see Chapter 8, section on "Pattern Initiators and Controllers").

Ganglion Cell Sensory Systems: Submodalities

The sensory ganglion cells of four sensory systems illustrated in Figure **11.3**D–F send their axons to primary sensory nuclei in the dorsal medulla. We are referring here to the ganglion cells of the *(a)* auditory system, which end in the cochlear nuclei; *(b)* vestibular system, which end in the vestibular nuclei; *(c)* gustatory system, which end in the rostral nucleus of the solitary tract; and *(d)* vagal/glossopharyngeal visceroceptive system, which end in the caudal nucleus of the solitary tract. These special sensory nuclei are all derived in the embryo from a highly differentiated, dorsal region of the primary hindbrain vesicle, the rhombic lip (see Chapter 6, section on "A Nervous System Flatmap for Animals"; also see Figs. 5.14 [in Chapter 5] and 6.8 [in Chapter 6]). Without going into details, these sensory nuclei generate axonal projections or pathways to the cognitive/cerebral (Fig. **11.4**), behavioral state, and motor systems.

Finally we come to the spinal nerve ganglion system associated with the spinal nerves and their serial homolog in the cranial region, the trigeminal ganglion. The sensory nuclei of the trigeminal nerve develop just below (ventral to) the rhombic lip in the embryo, and for all intents and purposes they represent a rostral extension into the brainstem of the corresponding regions of the spinal cord that receive inputs from the spinal nerve ganglia.

The spinal nerve ganglion system is commonly equated with the somatic sensory system, but the meaning of the latter term needs to be clear. Spinal nerve ganglia transmit sensory information from what is usually thought of as the soma or body (by and large the skin and skeletomotor system), as well as from the viscera. And in doing so, they transmit a rather diverse array of sensory modalities, including touch, pain, temperature (from hot to cold), muscle and tendon stretch, and the state of joints, ligaments, and fascia. Stretch receptors in muscle and tendon are unusual in that they participate in reflexes that control muscle tone, but their activity does not seem to reach the level of consciousness. In contrast, sensory information from the joints, ligaments, and fascia is important for elaborating the *kinesthetic sense*—the conscious awareness of body position in space. The splanchnic nerves (see Chapter 8, section on "The Autonomic Motor System") contain spinal nerve ganglion extensions that transmit a wide range of sensations from the viscera to the spinal cord, and then the brain. The splanchnic nerves also contain abundant preganglionic axons to the prevertebral autonomic ganglia, like the celiac ganglion (Fig. 8.12 in Chapter 8).

The peripheral ends of spinal nerve ganglion cells display a wide range of appearances, from completely unelaborated and naked ("free") to having elegant encapsulations by surrounding nonneuronal cells (Fig. **11.5**). In general, the simple peripheral extensions are associated with small spinal nerve ganglion cells, conduct action potentials slowly, detect thermal and painful stimuli, and preferentially reach the thalamus via the spinothalamic tracts (Fig. **11.4**a). In contrast, encapsulated peripheral endings are associated with large spinal nerve ganglion cells, conduct action potentials much faster, detect touch and stretch stimuli, and preferentially reach the thalamus via the dorsal column-medial lemniscal pathway (Fig. **11.4**b).

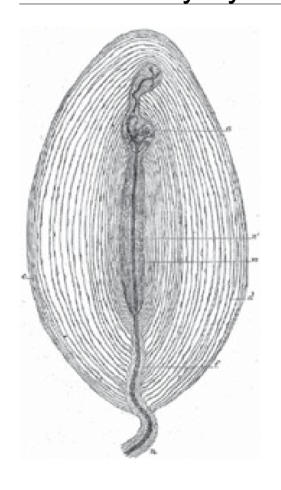


Figure 11.5
The histological structure of a Pacinian corpuscle, an encapsulated nerve ending that is a mechanoreceptor especially sensitive to vibration. The corpuscle is from the mesentery of a cat and is shown in longitudinal section; the lamellae are formed by specialized fibroblasts. The illustration is based on a drawing by Louis Ranvier, 1875. Key: a, region where one of the branches of the terminal fiber (dendrite) divides into many branchlets that go on to form abundant terminal elaborations; f, perineural sheath; m, central mass or inner bulb; n, nerve fiber (dendrite) leaving the capsule; n', terminal fiber (dendrite). From L.F. Barker, *The Nervous System and Its Constituent Neurones* (Appleton: New York, 1899, p. 395).

In other words, the "somatic sensory system" or spinal nerve ganglion system actually has a number of submodalities that have more or less distinct pathways within the spinal cord and to the cerebral cortex. Nevertheless, multimodal spinal nerve ganglion cells do exist, and there is extensive convergence of somatic and visceral inputs onto individual neurons at all levels of the spinal cord and brain. The situation is not so different in principle from the other major sensory modalities. There are main and accessory olfactory systems, there are visual "subsystems" for the four types of photoreceptors, and there are separate nerves and ganglia for the two major divisions of the inner ear, the cochlea and semicircular canals. In the end, each sensory modality has its own differentiations, though all of the major types establish more or less parallel pathways to specific, primary sensory areas of the cerebral cortex (Fig. **11.4**).

Affect: Pain and Pleasure, Emotion, and Mood

Motivation and emotion are two fundamental aspects of conscious experience that are standard topics in psychology, and they are making a comeback in respectable neuroscientific circles. There is a vast array of experimental data on the localization of neural mechanisms that subserve motivation and emotion, and yet in all candor it must be admitted that the basic organization of these mechanisms remains elusive and unknown. We broached the topic of motivation or drive in Chapter 8, under the discussion of motor pattern initiators. There it was suggested that intrinsic neural activity in the hypothalamus (either in the behavior control column or in the behavioral state system) plays an important role in motivation, although the crucial question of where the conscious perception of drive or motivation is elaborated remains unanswered. Is it cortical or subcortical?

Emotion leads us into the more general topic of affect or feeling. Today there is tremendous interest in the cognitive or thinking aspect of consciousness, although the affective aspect is really what separates us from machines like computers that are much better at logical operations than we are. A good case can be made for the proposition that all conscious experience is accompanied by affective tone, ranging from subtle feelings of comfort or discomfort to extreme emotions like rage and orgasm. What neural systems subserve affect, and where are the perceptions actually elaborated in the brain?

Perhaps a good place to start is with pain and pleasure. After all, they are the conscious reflections of punishment and reward, the reinforcement for learning whether to avoid or repeat a behavioral act. Behaviors associated with pain tend to be avoided in the future, and those associated with pleasure tend to be repeated. In addition, the organization of pain or nociceptive neural systems has been studied in great detail. As noted in the previous section, painful stimuli are detected by small sensory ganglion cells with thin, simple peripheral extensions (dendrites) to the body wall and viscera. These stimuli are transmitted to the brain from spinal neurons that generate the so-called spinothalamic tracts. In fact, the spinothalamic tracts have extensive projections in the brain, with offshoots to the brainstem reticular formation and periaqueductal gray and to the nucleus of the solitary tract and parabrachial nuclei, before ending widely in the thalamus. In addition, the tracts extend to innervate restricted parts of the hypothalamus, the cerebral nuclei, and even the medial prefrontal cortex.

All these terminations of the spinothalamic tracts are important. But for now we should note that terminal fields in the thalamus include the ventral posterior nucleus, which also receives touch information through the dorsal column system and projects to the classic somatosensory cortex (Fig. **11.4**); the posterior complex; and midline and intralaminar nuclei, which together have very widespread cortical projections. Overall, it is clear that the central nociceptive system involves many structures with an accompanying circuitry that is very complex. And if the elaboration of consciousness is a property of the cerebrum, there are many candidate cortical areas because of the widespread distribution of nociceptive information in the thalamus. Fortunately for neuroscience at least, people with lesions in various cortical regions have provided important clues as to where the perception of pain may be elaborated. This evidence, as well as very recent data obtained with functional imaging in neurologically intact, unanesthetized people, would suggest that pain is perceived as such in a cortical site that includes the prefrontal region and rostral half of the insular region. People with lesions involving this site report that they can feel they are being pinched or poked, but that it does not hurt.

Relatively little work has been done on pleasure systems in the brain. Perhaps the most interesting aspect of this problem began with a discovery of James Olds (1922–1976) in the 1950s—by pressing a lever, rats will voluntarily deliver electrical stimulation to certain parts of the brain via an electrode. Animals will self-administer this electrical stimulation of the brain thousands of times a day, to the exclusion of eating, drinking, and all other behaviors; and the neurosurgeon Robert Heath showed in the 1960s that people report pleasurable feelings akin to orgasm when electrical stimulation is self-administered to certain forebrain sites (especially in the septal region). Apparently this experimental procedure taps into a pleasure system of the brain.

It now appears that the pleasure system accessed by the electrical self-stimulation paradigm involves pathways stretching between the prefrontal cortex and ventral cerebral nuclei, through the lateral hypothalamic area, and into medial regions of the midbrain and pons. One reason for medical interest in this system is the anhedonia or loss of affect associated with clinical depression. Analogous to the clinical data just discussed for pain, it has been found that lesions in the medial prefrontal cortex can produce anhedonia in people, and recent functional imaging studies also tend to confirm this localization. Even more recent data indicate that deep brain stimulation in the ventral medial prefrontal cortex may relieve the symptoms of clinical depression.

Taken together, available evidence currently suggests that the perception of pain and pleasure is elaborated in a band of cerebral cortex that includes the medial prefrontal region and caudally adjacent parts of the insular region. This is especially interesting in view of the fact that visceral and nociceptive information from the nucleus of the solitary tract and parabrachial nucleus reaches this same band of cortex via both direct projections and projections relayed through the thalamus. Think about what an emotional

experience is from an introspective point of view. Emotional experiences are "from the heart" or "from the gut." Visceral sensations are virtually synonymous with emotion. They involve changes in the perception of heart rate, breathing, and body temperature. The most obvious explanation is that they involve perception of visceral sensations.

Thus, the conscious perception of pain, pleasure, and emotions may be elaborated in a band of prefrontal-insular cortex. Based on known axonal connections of this cortical band, it seems obvious that neural activity there can be influenced either by sensory inputs or by inputs from association cortical areas. Thus, affective experience may be evoked either by sensory inputs or by activity in association cortex (for example, during thinking or dreaming).

Moods are different. They have much longer durations that stretch into days and weeks, rather than being transitory affective responses to one type of stimulus or another. And mood tends to be stable, almost as if a setpoint has been changed. There is, of course, no known explanation for the regulation of mood in terms of neural systems. However, it seems reasonable to suggest that activity in one or more of the behavioral state control nuclei that project to the prefrontal-insular region of the cerebral cortex (see Chapter 9, section on "Modulating Behavioral State"; Fig. 9.5) plays a critical role. And recent experimental work indicates that an intracerebral neural network involving bidirectional connections between the prefrontal-insular cortex, the basal and central amygdalar nuclei, and the hippocampal formation is responsible at least in part for mediating learned emotional responses. From what has been said, it seems clear that the outlines of neural systems that elaborate affect are gradually coming into focus, but they are much more enigmatic than the classic sensory systems involving vision, audition, touch, and taste.

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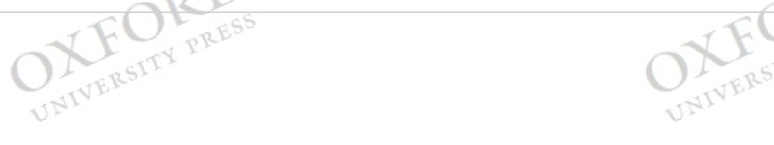






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> *“Current methods and ideas are entirely dependent on continuing progress in chemistry and physics, which remain the principal allies of the naturalist.”*
>
> Santiago Ramóny Cajal (1909)

While it can be useful to think of the brain as a biological computer, it is a grave mistake to think about the brain's circuitry in terms of hardwired computer chips. In the first place, because of the chromosome mixing that accompanies sexual reproduction, every brain is different in detail, just as every face is unique. And second, the brain is an organ composed of tissues and as such is alive and constantly changing, replacing, and repairing. It was a major breakthrough in late twentieth-century neuroscience to realize that the chemistry of synaptic transmission is very dynamic, that new neurons may be generated in adult mammals, and that it may become possible to regrow damaged axonal pathways within the adult central nervous system.

The topic of neural plasticity is vast, and it will only be touched on here to emphasize with selected examples the principle that brain architecture is far from static. The structure of the brain is constantly changing due to influences from the internal and external environments, and due to genetic factors associated with the normal life cycle of development, childhood, puberty, adulthood, and aging. To think about this more clearly, it us useful to return to the concepts of macroconnections, mesoconnections, and microconnections introduced in Chapter 6.

The macroconnections of the nervous system can be thought of as the gross anatomy level of organization. Included here are the basic parts: the major gray matter regions (nuclei, cortical areas, and so on) and the major white matter tracts that interconnect them. The macroconnections—the macronetwork if you like—is laid down during embryogenesis by a genetic program that has evolved in a unique way for each species. The nervous system of each species has a unique and characteristic macroarchitecture, just like the body as a whole. This is how species were originally defined (Chapter 2). Every individual of a species is different, but those differences are within a narrow range compared to differences between species, and it is a general principle of classification (taxonomy) that only features generally applicable to all members of a taxon (for example, a species or a phylum) are taken into account; individual variation is not an issue.

Mesoconnections deal with the nervous system's wiring diagram at the level of neuron types, which in vertebrates are typically populations of neurons that share a set of features, much like an animal species is defined—for example, Purkinje, granule, basket, stellate, and Golgi cells in the cerebellum. So the mesoconnections of a species are also genetically hardwired, although there is individual variation in the quantitative aspects of this hardwiring. For example, there is commonly a range in the absolute number of neurons in a population making up a neuron type in a particular species.

Then there are the miroconnections, which deal with individual neurons and the quantitative synaptic relationships they establish among themselves. The absolute numbers of axon collaterals and dendritic spines, the absolute strength of individual synapses, and so on are different in every individual and change dynamically throughout life. This is the level of analysis where modifiability of the nervous system is analyzed most profitably from the standpoint of underlying mechanisms rather than simple description and correlation.

In summary, each species has characteristic nervous system macroconnections and mesoconnections that are genetically hardwired during development, and each individual within a species has unique nervous system microconnections that change dynamically throughout life.

Learning: Changing Synaptic Strength

In the late nineteenth century, Cajal discovered how nerve cells interact with one another in the adult brain: an axon terminal comes into contact or contiguity with a dendrite or cell body. Very quickly he realized that learning might be explained by changes in the strength of these functional contacts (synapses), in a way analogous to how muscle cells become stronger with use or exercise. Tremendous progress has been made in the last several decades toward understanding the cellular and molecular underpinnings of changes in synaptic strength.

It is convenient to start with the observation that there are two fundamentally different classes of learning: associative and non-associative. *Habituation* is an example of *nonassociative learning*. In many cases, when a particular stimulus is presented over and over again, the magnitude of the stereotyped response to that stimulus progressively decreases. Then, if there is a long gap of time before the stimulus is presented again, a response as large as the first one is elicited. This simple type of learning is common to amoebas and humans. In animals with a nervous system it appears to involve a transient *weakening* of synaptic strength, whereas the converse response, *sensitization*, appears to involve a transient *strengthening* of synapses.

Associative learning is different, and it at least requires a nervous system. Experimental psychologists have traditionally distinguished between two broad types of associative learning: classical and instrumental. *Pavlov, who won the first neuroscience-related Nobel Prize, in 1904, made classical conditioning or learning famous*. The principle here is that certain stimuli reliably elicit a stereotyped response. For example, the sight of food (an unconditioned stimulus) elicits salivation (an unconditioned response) in a dog. On the other hand, the ringing of a bell normally does not elicit salivation. However, if the ringing of a bell is paired in time with the sight of food—specifically, if it is rung *just before* the sight of food—the dog learns (associates) to salivate when it hears just a bell but does not see the food. The sound of the bell has become a conditioned stimulus that leads to a conditioned response. As discussed in Chapter 8 (section on “The Cerebellum”), Richard Thompson and his colleagues have made great progress in clarifying the organization of neural networks that mediate classical Pavlovian learning. A key site for synaptic plasticity has been identified in the deep cerebellar nuclei, although exact molecular mechanisms remain to be clarified.

Instrumental conditioning or learning was made famous by B.F. Skinner (1904–1990) of Harvard. In this case an animal or person must do something actively and experience the consequences of the behavior via feedback. For example, an exploring rat might eventually press a lever in its laboratory cage for the first time (and for no apparent reason)—and unexpectedly receive a tasty morsel to eat. The animal quickly learns that pressing the lever delivers something good to eat. This is reinforcement learning. The subject actively does something (expresses a behavior) and then receives as feedback positive (pleasant) or negative (unpleasant) reinforcement, a reward or a punishment (see Fig. 7.5 in Chapter 7). This association of pain or pleasure with the execution of behavioral acts is a powerful determinant of future behavior—whether particular behavioral acts will be repeated or avoided. One of the main differences between classical and instrumental conditioning is that the former involves a passive situation. The animal or person is simply exposed to two stimuli (unconditioned and conditioned), and over the course of one or more trials a conditioned response is learned. In contrast, instrumental conditioning requires active participation of the subject, who must voluntarily initiate a behavioral act and then receive feedback about the results. The subject is *instrumental* in initiating the learning event.

The organization of neural networks that mediate instrumental leaning is not nearly as well understood as that for classical learning. However, because voluntary initiation of behavior is critical for instrumental learning, it seems very likely that the critical site of synaptic plasticity is in the cerebrum (Chapter 10), rather than the cerebellum. Unfortunately, the link between positive and negative reinforcement systems (pain and pleasure systems discussed in Chapter 11, section on “Affect”) and cerebral synaptic plasticity remains obscure.

The best model for studying the chemistry of synaptic plasticity, and the possible role of modified gene expression associated with learning, is a phenomenon called *long-term potentiation* (LTP). It has been exploited most thoroughly in the hippocampal cortex, which seems to play an important role in learning spatial information, for example, about the environment during exploratory or foraging behavior. However, LTP is found in many other parts of the nervous system, including autonomic ganglia, where a form of it was discovered by Larrabee and Bronk in 1947. Work on the hippocampus began in 1973 when Bliss and Lømo basically showed that the postsynaptic response to an action potential is enhanced or potentiated if it is preceded by an appropriate burst of action potentials. In other words, under the right conditions involving the right neuron types, postsynaptic responses can be greatly augmented by preceding patterns of action potentials, with the correct timing. Short-lasting augmentation associated with sensitization, for example, had been known for some time. What made LTP unusual was its long duration. In intact rats, hippocampal LTP can last for at least months.

The chemical underpinnings of LTP have proven to be very complex, and sometimes different in different classes of synapses. In fact, the actual long-lasting biochemical change ultimately responsible for enhanced synaptic transmission remains elusive. However, certain initial stages of the process are clear. For example, it seems certain that the biochemical changes are triggered by increased entry of Ca^{++} ions into the postsynaptic compartment, and that these ions may enter through special glutamate-sensitive receptors (NMDA receptors) that only open when the postsynaptic membrane is depolarized (for example, by a train of action potentials).

The bottom line is that there are many mechanisms for changing the strength of synapses with use, and it is entirely possible that the efficacy of transmission at all synapses is subject to modification by use. These cellular mechanisms range from habituation and sensitization, through tetanic and posttetanic potentiation, to long-term potentiation and depression. They are electrophysiological measures of synaptic plasticity. It is important to end this section with the observation that LTP may also be accompanied by morphological changes. There is evidence to suggest that LTP is accompanied not only by changes in the shape of synapses (for example, larger postsynaptic densities, which imply more effective synaptic transmission) but also by an increase in the number of synapses, or at least synaptic densities. Thus, there is increasing evidence that at least some forms of learning are accompanied by changes in the brain's physical microconnections.

Stress: Biochemical Switching

Stress has been defined as any condition that perturbs bodily mechanisms from their normal equilibrium state. Curiously, a very good empirical definition of stress has turned out to be any stimulus or condition that elicits secretion of ACTH from the pituitary gland, and thus the release of glucocorticoid steroid hormones (for example, cortisol) from the cortex of the adrenal gland into the blood (Fig. 8.14 in Chapter 8). There is an essentially infinite set of conditions that produce stress, from exposure to a hot or cold environment, to confrontation with a predator, to public speaking. Yet despite the fact that dealing with each one of these situations requires a unique, customized set of responses, they all share one feature: increased blood levels of glucocorticoid hormones. As the name implies, one of the important effects of these hormones is to raise blood levels of glucose, thus helping to supply more energy for reacting successfully to the stressful situation.

The hypothalamic-pituitary-adrenal axis is a classic example of negative feedback control in a neuroendocrine system (Fig. 8.14 in Chapter 8). The basic idea is that high circulating levels of adrenal glucocorticoid hormones feed back on the hypothalamus to decrease the synthesis and release of CRH, the hypothalamic peptide hormone/neurotransmitter that secretes ACTH from the anterior pituitary gland—and low levels of circulating glucocorticoids have the opposite effect; they lead to increased synthesis and release of CRH. This arrangement serves to maintain relatively constant levels of circulating glucocorticoids.

Glucocorticoids have two important features in this scenario. First, being lipophilic they cross the blood–brain barrier and thus gain unimpeded access to the brain from the blood. And second, they have widespread effects on gene expression via nuclear glucocorticoid receptors, which bind to regulatory regions of DNA when occupied by hormone. After Wylie Vale and his colleagues identified CRH and raised specific antibodies to it in the early 1980s it became possible to examine experimentally the hypothalamic-pituitary-adrenal axis with immunohistochemical (and later on with hybridization histochemical) methods. On a very basic level it has been found that glucocorticoids exert a profound inhibitory effect on expression of the CRH gene, and on levels of CRH peptide in hypothalamic neuroendocrine CRH neurons, in the paraventricular nucleus. This was not surprising, but unexpectedly it was found that these neurons express two additional neuropeptide genes when glucocorticoid negative feedback is removed. These are the genes for vasopressin and angiotensin II, both of which stimulate secretion of ACTH. Thus, when blood levels of glucocorticoids are chronically low, neuroendocrine CRH neurons cosynthesize three ACTH secretagogues, which act synergistically and thus very powerfully on ACTH release.

These results indicate that glucocorticoid hormones can dramatically alter the ratio of neuropeptides synthesized and shipped down the axon of individual neurons. However, the situation with CRH neuroendocrine motor neurons is much more remarkable and interesting than this. It is now known that this one neuron type can express more that 10 different neurotransmitters, and immunohistochemical and hybridization histochemical methods have been used to show that each type of stress that an animal is exposed to produces a different ratio of these neurotransmitters within this neuron type. In other words, the complement of peptide neurotransmitters found in CRH neuroendocrine motor neurons at any particular time is a function of the history of the animal—what stressors it has been exposed to over the course of the last several days. This result might not seem surprising in light of our earlier comment that each type of stressful condition requires a unique set of physiological and behavioral responses. However, the actual functional consequences of having different complements of neurotransmitters in a neuron at different times are much more difficult to determine experimentally.

CRH neuroendocrine motor neurons provide a fascinating model for testing predictions about the functional consequences of altered ratios of neurotransmitters within individual neurons. In addition to expressing more than a dozen potential neurotransmitters (including glutamate), the axon of these neurons does almost everything that an axon can do (Fig. **12.1**). First, their main axonal output is to the median eminence, where their axon terminals release whatever complement of neurotransmitters are available into the portal circulation for delivery to the anterior pituitary (Figs. 8.14 and 8.15 in Chapter 8). This is a hormonal function. In addition, some of the transmitters released in the median eminence bind to receptors on nearby axon terminals (*presynaptic receptors*). For example, CRH appears to inhibit the release of GnRH in the median eminence of rats. This

is a paracrine effect of CRH on GnRH-containing axon terminals. And finally, on their way to the median eminence, CRH neuron axons generate terminals-of-passage within the lateral hypothalamic area. This in all likelihood represents a classical synaptic function of this CRH neuron type. Thus, CRH neuroendocrine motor neurons are in a position to mediate synaptic, paracrine, and endocrine effects on different cell types in the lateral hypothalamic area, median eminence, and anterior pituitary, respectively.

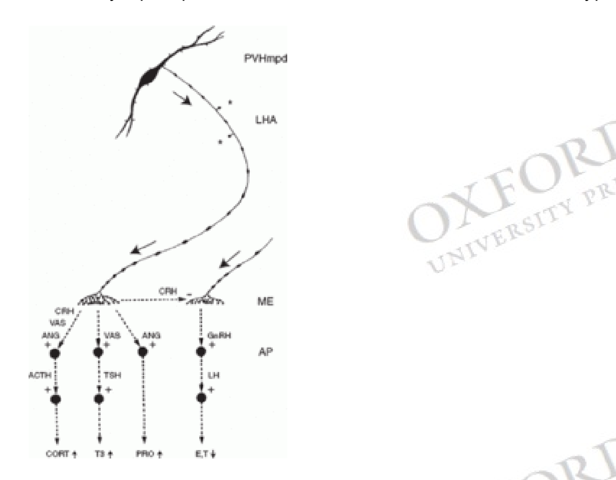




Figure 12.1
The basic morphology of a typical CRH neuroendocrine motor neuron in the hypothalamic paraventricular nucleus (its dorsal part of the medial parvicellular division; PVHmpd). The axon trunk ends as a spray of terminals (telodendron) in the external layer of the median eminence (ME), although terminals (synapses) of passage occur along the axon in the lateral hypothalamic area (asterisks). In the median eminence, neurotransmitters can have two actions. First, they can diffuse to nearby axon terminals with appropriate presynaptic receptors (say, for CRH) and exert paracrine effects. Second, they can enter the hypophysial portal circulation and be transported to the anterior pituitary gland (AP). In this way, three of the neuropeptides released by these neurons can directly or indirectly (via paracrine effects at the median eminence level) influence the secretion of hormones from four cell types in the anterior pituitary. Key: ACTH, adrenocorticotropic hormone; ANG, angiotensin II; CORT, cortisol/corticosterone; CRH, corticotropin-releasing hormone; E, estrogen; GnRH, gonadotropin-releasing hormone; LH, luteinizing hormone; PRO, prolactin; T, testosterone; T3, thyroid hormone; TSH, thyroid-stimulating hormone; VAS, vasopressin. Adapted with permission from L.W. Swanson, Biochemical switching in hypothalamic circuits mediating responses to stress, *Prog. Brain Res.*, 1991, vol. 87, p. 192.

We have suggested that this arrangement could result in the *biochemical switching* of information flow through an anatomically fixed neural network (see Fig. **12.1**). First let's examine the hormonal effects of CRH on the anterior pituitary. Under chronically high levels of circulating glucocorticoids (as in Cushing disease), CRH neurons are making little or no vasopressin and angiotensin, and only moderate amounts of CRH. Here, a given number of action potentials will release some CRH, and little or no vasopressin and angiotensin. This will lead to modest release of ACTH, and thus adrenal glucocorticoids. In contrast, under chronically low levels of circulating glucocorticoids (as in Addison disease), high levels of CRH, vasopressin, and angiotensin II will be synthesized and relatively large amounts will be released by the same number of action potentials. This will lead to very high levels of ACTH release, but it will also lead to thyroid-stimulating hormone release as well because vasopressin is also secretagogue for this anterior pituitary hormone. In addition, prolactin will be secreted because angiotensin II is a secretagogue for this hormone as well. Thus, for one hormonal condition CRH neurons will release ACTH and for another condition it will release ACTH as well as thyroid-stimulating hormone and prolactin.

But what about all of the other neurotransmitters synthesized by these CRH neurons? Two of them are of particular interest here, enkephalin and neurotensin. They are interesting because there appear to be no receptors for these peptides in the anterior pituitary. Instead, there are enkephalin receptors in the median eminence (presynaptic receptors on axon terminals) and neurotensin receptors in the lateral hypothalamic area. Thus, one could reasonably hypothesize that these CRH neurons synthesize a number of transmitters in part because there are different complements of receptors at the various sites where their neurotransmitters act. For example, neurotensin may exert postsynaptic effects on neurons in the lateral hypothalamic area, but no effects in the anterior pituitary, where receptors are lacking. The concept of biochemical switching of information flow in neural networks is easy to appreciate in the lateral hypothalamic area. All things being equal, this synapse will not function if transcription of the neurotensin gene has been inhibited for any length of time, and only neurotensin receptors are expressed postsynaptically. Or put another, more likely, way, the efficacy of this synapse may depend on how expression of the neurotensin gene is regulated.

In the case we have been considering, a particular steroid hormone produces reversible effects on expression levels of a set of neuropeptide genes in a particular neuron type. However, there is now a vast literature showing that other hormones, as well as neurotransmitters released from axon terminals, can regulate the expression of neurotransmitters as well as of neurotransmitter receptors in many regions of the nervous system. Furthermore, each experimental manipulation of the animal seems to produce a unique, "signature" pattern of gene expression changes in the nervous system. It turns out that there is constant, extensive biochemical plasticity in neural networks. Exactly how this influences information processing ("computing") in these networks remains largely unknown.

Cycles: Circadian and Reproductive

In Chapter 9 we discussed circadian and reproductive rhythms, and it is now clear that they are accompanied by changes in gene expression potentially related to the efficacy of synaptic transmission. The implication here, as in the preceding section, is that information processing in neural networks is not simply a product of action potential patterns. Information processing may also be influenced by changes in the availability of neurotransmission-related molecules as determined by altered levels of corresponding gene expression. For example, there is a clear circadian rhythm of CRH gene expression in paraventricular neuroendocrine motor neurons, and there are also clear circadian rhythms of neuropeptide gene expression in the suprachiasmatic nucleus itself (the primary endogenous circadian clock of the brain).

Another example of changing gene expression patterns under natural conditions involves the female reproductive cycle in rodents, where it has been examined most carefully. The approximately 4-day estrous cycle in female rats was discussed in Chapter 9 (section on "Reproductive Cycles"), where it was pointed out that the animals go into heat once every 4 days, around the time of the cycle when ovulation takes place. This coordination of behavioral receptivity and ovulation maximizes chances of egg fertilization through sexual intercourse, and it is driven by a surge of estrogen controlled by the hypothalamus. It was pointed out that the estrogen surge produces a major shift in the female's behavior, from defending against the advances of males to actively soliciting a partner for mating. It takes about 8 hours for the effects of estrogen to be manifest, and they are almost certainly due to effects of the steroid hormone on some aspect(s) of neurotransmission-related gene expression in the sexually dimorphic system of the forebrain.

Exactly how estrogen produces these specific changes in behavior is not known. However, clear examples of estrogen effects on neuropeptide gene expression in the sexually dimorphic system over the course of the estrous cycle have been demonstrated. For example, the neuropeptides substance P and cholecystokinin are coexpressed in neurons of three interconnected parts of the system (medial amygdalar nucleus, bed nuclei of the stria terminalis, and medial preoptic nucleus) and over the course of the estrous cycle substance P levels stay constant in these neurons whereas cholecystokinin only becomes detectable on the day of estrus. In other words, ratios of coexpressed neurotransmitters change dramatically within individual neurons of the sexually dimorphic system during the course of the female reproductive cycle due to changing levels of

estrogen in the blood. This is another example of potential biochemical switching or biasing of information flow through a functionally specific neural network.

Damage Repair: Regrowth

Perhaps the most dramatic examples of dynamic architecture in the adult mammalian nervous system involve responses to damage and disease. This is another vast topic that we simply broach here because of its critical importance from the medical standpoint. First and foremost, there is a basic difference between damage repair in the peripheral and central nervous systems. When a peripheral nerve is cut, the distal end inevitably degenerates, of course (Appendix C). However, if a skilled surgeon unites the severed halves of the nerve carefully, the intact (central) stump of the nerve can regrow along the old pathway to the original innervation fields, and sensation can be restored. This regeneration is more successful the closer to the periphery the cut has been made.

The situation is quite different in the central nervous system, where lesions, destruction, or death of neurons rarely leads to any significant regeneration of previously intact networks. One reason for this unfortunate situation is the extreme complexity of the brain. Regrowing axons would have to navigate an unbelievably complex labyrinth of neural tissue to find their original targets. The other impediment may prove to be more tractable. When central neural tissue is damaged, a “glial scar” forms in the region. It is produced by the massive proliferation of supporting cells (primarily astrocytes) that remove damaged tissue through phagocytosis. In addition, however, cells of the glial scar may secrete factors that inhibit the growth of axons.

It has been known since the nineteenth century that damaged neurons in the brain attempt to regrow their axons. Unfortunately, these axonal sprouts typically do not grow very far. Somewhat more success has been obtained by transplanting certain neurons into the damaged brain. For example, certain transplanted aminergic neurons (see Chapter 9, section on “Modulating Behavioral State”) can send new axons rather long distances through the brain. In all these cases, however, it is important to determine whether newly generated axons in the adult brain establish correct or incorrect synaptic relationships. Do they reestablish connections that were damaged, or do they establish new connections that in essence form aberrant networks? The latter situation could well be worse than no repair at all. This is one of the basic conundrums of experimental neurology—how to repair damaged neural networks without creating more harm than good, more side effects than benefits. The structural complexity of the central nervous system is a formidable opponent.

Perhaps the greatest hope for repairing the damaged adult nervous system lies in understanding the cell and molecular biology of nervous system development. The goal here is to take advantage of molecular mechanisms responsible for building neural networks in the embryo. Perhaps they can be reinitiated or mimicked in the adult to rebuild or repair damaged networks.

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Brain Architecture (2 ed.): Understanding the Basic Plan

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Genome and Connectome

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"It is not a little remarkable that what is definitely known regarding the special functions of the nervous system has been ascertained within the last thirty years."

British and Foreign Medical Review (1840)

"Although I disapprove the ludicrous 'scientific' attitude displayed by many 'molecular biologists' and believe that their extravagant shenanigans deserve a full measure of ridicule, I nevertheless consider their specialty to be an important field of biology."

Hartwig Kuhlenbeck (1973)

So far we have outlined the cellular composition of the nervous system, the spatial relationships of its basic parts, and the network arrangement of its four basic functional systems. This is classical neuroscience. Like any organ, the brain has a regional architecture and a number of functional systems, in this case motor, cognitive, state control, and sensory. The global architecture of the vertebrate nervous system seems to be based on the principle of segmentation, with particular neuromere segments differentiating to different extents in different groups of animals. Perhaps the most critical factor in this differentiation is the overall body plan of a particular animal group. But within this basic plan the fundamental building block or component of all neural networks remains the neuron, which has the same basic cell and molecular biology in all animals with a nervous system. What varies between species is the way neurons are used to build the neuromeres, or alternatively the way neurons are used to construct neural subsystems within the system as a whole.

There is, however, a seemingly very different way of looking at adult nervous system function: in terms of chemical systems, and at a more basic level gene expression patterns and gene expression control networks. This point of view is concerned at a superficial level with how drugs act on the brain—and how altered gene expression patterns influence nervous system structure and function. The basic conundrum here is that very often a drug acts, or the expression of a gene is altered, in a complex way that cuts across multiple functional systems. For example, acetylcholine is a neurotransmitter in somatic motor neurons of the spinal cord, in parasympathetic ganglia of the visceral organs, in magnocellular neurons of the basal forebrain, and in striatal interneurons. Therefore, the enzyme that synthesizes acetylcholine is expressed in specific neuron groups that are nevertheless parts of quite different functional systems. Expression of the gene for this enzyme is regulated in a very neuron-specific way, but the neuron groups involved are not related in any known way to a particular functional system. In other words, quite possibly there is no direct correspondence between the organization of functional systems in the brain and the regulatory networks that determine global patterns of gene expression.

If this is true, then certain basic conclusions follow. For example, if there is no relationship between adult functional neural systems and gene expression systems or patterns, then drugs will typically act on multiple functional systems, and the altered expression of any single gene will typically occur in multiple functional systems. If true, it also follows that gene expression patterns cannot reveal anything basic about the organization of functional neural systems or even about the identity of neuron types.

Whether or not there is a basic relationship between adult functional neural systems or networks and gene control networks, two things are clear. First, as discussed in earlier chapters, a genetic program obviously constructs the nervous system during embryogenesis, whether or not this is done along functional system lines. And second, it is critical to appreciate that the functional and pharmacological/genomic systems of the brain are equally important in their own rights, whether or not they are causally interrelated in the adult. The practical implications for no relationship are that, generally speaking, individual drugs typically will have multiple side effects (effects on multiple systems other than the intended target), and the effects of genetically engineering the expression of a particular gene typically will be complex and multifunctional. At the moment, examples of highly specific drug action or highly localized gene expression in one (and only one) particular functional system are certainly known, but they are exceptions to the general rule.

Today, the 3 billion base pairs of the human genome have at least in principle been sequenced—which took almost exactly 50 years (and $3 billion from the Human Genome Project) after the molecular structure of DNA was elucidated by James Watson and Francis Crick at Cambridge. Of course the task of decoding the sequence has now begun in earnest, and the results of this enterprise ultimately will resolve the problem of whether and how neural networks are related to gene networks. Nevertheless, the sequencing itself has major theoretical as well as technical implications. On the theoretical, computational, or modeling side, we know that there are on the order of 20,000 genes in the mammalian genome (with well over half expressed in the brain). This knowledge is fundamentally important because we now have boundary conditions on the problem of gene network complexity. In principle we can know what all of the genes are—what all of the players are—and we have begun to classify them functionally. It is only a matter of time before the function of all the genes will be known, and they will be classified in an orderly way. On the technical side of the coin, this knowledge allows us in principle to measure how the entire genome is expressed over time in any particular part of the brain, and under any conditions, we are interested in.

One goal of molecular biology is to understand how the network of 20,000 genes in the chromosomes of each cell is regulated as a whole over the course of time. It now seems

certain that expression in the gene network is modulated by the combinatorial action of an exceptionally rich set of regulatory (transcription) factors. The difficulty will come in trying to determine experimentally the kinetics and temporal sequencing of this regulation. In the end, however, we are faced with a problem in complex systems analysis.

The architecture of the brain is also, as we have seen, a problem in complex systems analysis. How complex is the nervous system? By one measure, it has been estimated that on the order of 100,000 macroconnections form the mammalian nervous system—as compared to roughly 20,000 genes in the genome. It is hard even to imagine at this point in time how two systems as different and complex as these might be compared in a systematic and meaningful way. Nevertheless, success of the Human Genome Project inspired the start in 2010 of a Human Connectome Project, which aims ultimately to determine systematically a complete connection table for the human brain—a task orders of magnitude more difficult than just sequencing the chromosomes.

In the twenty-first century, systems neuroscience will be transformed by molecular biology in ways that would be foolish even to speculate about. We are in the early stages of a revolution as transforming as the introduction of the cell theory in the middle of the nineteenth century. If history is any guide, we can expect that the fundamental contributions of molecular biology to the architecture of the brain will come from two sources. One source will involve comparative studies of much simpler organisms, and the other will involve experimental analysis of early mammalian development, when neural macrocircuitry literally is being constructed by a genetic blueprint or program that remains to be decoded or reverse engineered. It will be exciting to see whether molecular biology ends up basically confirming 2500 years of thinking about the architectural plan of the brain, whether it provides a radically different interpretation, or whether it proves to be irrelevant. Whatever the outcome, there is no lack of enthusiasm for attempting the quest.

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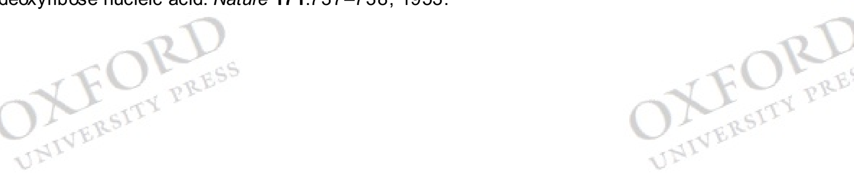
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Describing Position in the Animal Body

"No matter how objective and simple it may appear, all description relies on personal interpretation—the author's own point of view… From another perspective, observation provides the empirical data used to form our conclusions, and also arouses certain emotions for which there are simply no substitutes—enthusiasm, surprise, and pleasure, which are compelling forces behind constructive imagination. Emotion kindles the spark that ignites cerebral machinery, whose glow is required for the shaping of intuition and reasonable hypotheses."

Santiago Ramón y Cajal (1916)

It would seem to go without saying that anatomy is critically dependent on the unambiguous description of physical relationships. Therefore, it is both surprising and confusing to find how difficult it is to read the neuroanatomical literature. It is bad enough, as we shall see in Appendix B, that names for the parts are not standardized. But it is very disconcerting that even words used to describe position within the central nervous system are often ambiguous. For example, whereas in geography the meanings of north, south, east, and west are universally understood, the terms anterior and posterior often have contradictory meanings in embryology, comparative anatomy, and human gross anatomy.

Why is there such confusion about describing position or location in neuroanatomy? Many factors are undoubtedly involved, but the most important is probably tradition. From classical Greek times through the end of the eighteenth century, overwhelming interest was in the structure of the human body. Unfortunately for descriptive anatomy, we are somewhat unusual in our typical bipedal mode of locomotion, and this upright posture—as compared to quadrupeds, snakes, and fish—has led to the development and use of an idiosyncratic terminology for human anatomy. The obvious long-term solution has been emphasized in the earlier chapters of the book, and it falls back on the time-honored comparative and embryological approaches. Positional descriptors are most clear and unambiguous when they refer to the idealized relationships observed in the "typical vertebrate body plan" (Fig. **A.1b**), and in the "straightened-out embryo" (Fig. **A.1d** lower right).

One beauty of this approach is that the same simple, clear set of positional descriptors can be applied to all vertebrates (and all bilaterally symmetrical invertebrates as well) —rostrocaudal, dorsoventral, and mediolateral. But for now, when reading the literature one needs to infer positional meaning from context and a little background knowledge. Readers interested in pursuing this topic in depth should consult the references listed at the end of the Appendix. The following is an introductory overview.

To begin with, the body of all animals with a nervous system—whether invertebrate or vertebrate, whether radially or bilaterally symmetrical—has two orthogonal axes: longitudinal and transverse (Fig. **A.1a,b**). Then, in bilaterally symmetrical animals the longitudinal axis itself has two orthogonal axes (Fig. **A.1b**). At this point a critically important concept enters: bilaterally symmetrical bodies are most accurately described in terms of three perpendicular *axes* along with three corresponding *planes* (Fig. **A.1b** bottom).

The *axes* (rostrocaudal, dorsoventral, and mediolateral) are a little like the north-south and east-west lines on a compass. They are perpendicular to one another. It is possible to go a certain distance north or south, just as one can progress a certain distance rostral or caudal. Because the body is a three-dimensional object, rather than a surface (of the earth), three rather than two axes or cardinal directions are needed. They correspond conceptually to the x, y, and z axes of Cartesian geometry.

Now imagine an adult human standing up (Fig. **A.2** lower right). In humans, the "back" of the body, the dorsum, is traditionally referred to as posterior, whereas the "front" or belly, the ventrum, is traditionally referred to as anterior. So in the spinal cord gray matter, for example, one typically refers to anterior horns in humans and to ventral horns in other animals. This can be very confusing because some embryologists insist on referring to the rostrocaudal axis as the anterior-posterior axis.

In human anatomy one also traditionally refers to structures toward the head as superior (toward the heavens) and those toward the feet as inferior (toward the earth). This convention inspired the names of certain structures in the human brain—a good example we will mention shortly is the superior and inferior colliculi of the midbrain tectum—that make no sense in comparative neuroanatomy.

In comparative anatomy there are three standard *planes* that are perpendicular to one another, and that cut through the body or unfolded embryo: a *transverse* plane, and two *longitudinal* planes (*sagittal* and *frontal*). In Cartesian geometry they would be equivalent to x, y, and z planes. The sagittal plane is the same in all bilateral animals, including humans. It is the longitudinal plane that cuts the body into right and left pieces when viewed from above (Figs. A.1b and A.2 dorsal view). The *midsagittal* plane of course runs down the median plane (midline) and cuts the body into right and left halves. Proceeding laterally from the median plane creates *parasagittal* planes. Now the confusion begins. In humans, a series of planes proceeding from superior to inferior (in the standing subject) is referred to as "horizontal," which in context makes perfect sense. However, in comparative anatomy, where one most commonly deals with quadrupeds, fish, and snakes, the "horizontal" plane has a completely different meaning. Here it is the longitudinal plane that is perpendicular to the sagittal plane, and so it also has a rostrocaudal orientation. In animals the "horizontal" plane is parallel, not perpendicular, to the back (dorsum). Because of this, the third standard plane—*frontal*—must also have a fundamentally different meaning in human and in comparative anatomy.

To solve this basic dichotomy, a few perceptive anatomists have long advocated abandoning positional terms that refer to external reference points (like the horizon, or the

heavens and earth—superior and inferior) and adopt for all animals (including humans) positional terms referring to internal reference points (as in Figs. **A.1** and **A.2**). It is hard to predict how long this terminological standoff will persist. On one side are the comparative anatomists who are dealing with evolving general principles, and on the other side is the medical community, which is very influential and conservative, and understandably anthropomorphic.

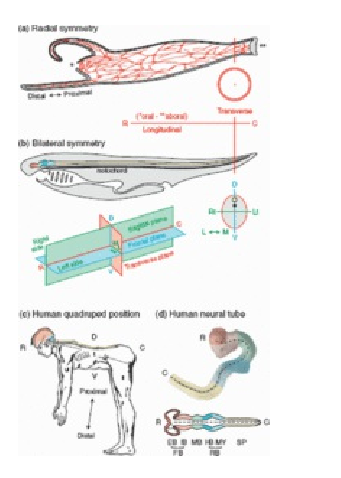






Figure A.1
General principles of describing positional information with a uniform system in all animals from hydra to humans. (*a*) Basic longitudinal (oral-aboral) and transverse axes in a radially symmetrical animal (hydra). (*b*) The three basic axes and planes in bilaterally symmetrical animals, here illustrated with a prototypical vertebrate. (*c*) Human body in the comparative anatomical position, where application of the planes and axes illustrated in *b* is easy to see. (*d*) Longitudinal axis (dashed line) of the neural tube in the human embryo, in the intact embryo (top), and in an artificially straightened embryo (bottom); compare with Figure 5.14. Key: *, oral end of body; **, aboral end of body; C, caudal; D, dorsal; EB, endbrain; FB, forebrain; HB, hindbrain; IB, interbrain; Lt, left; MB, midbrain; MY, medulla (afterbrain); R, rostral; RB, rhombicbrain; Rt, right; SP, spinal cord; V, ventral. Part *b* (top) adapted with permission from A.S. Romer, *The Vertebrate Body*, fifth edition (Saunders: Philadelphia, 1962, p. 3); part *c* adapted with permission from J.P. Schadé and D.H. Ford, *Basic Neurology* (Elsevier: Amsterdam, 1965, p. 15); part *d* (top) adapted from M. Hines, Studies on the growth and differentiation of the telencephalon in man *J. Comp. Neur.*, 1922, vol. 34, p. 124.

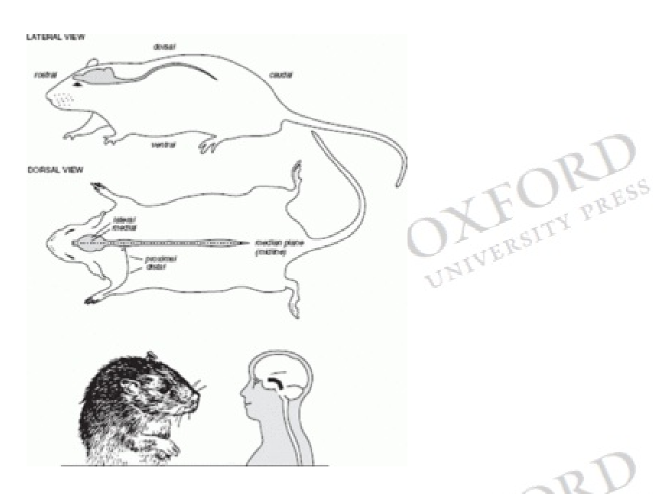




Figure A.2
How to describe position or location in the rat and human; see text and Figure **A.1** for context. Reproduced with permission from L.W. Swanson, *Brain Maps: Structure of the Rat Brain*, second edition (Elsevier: Amsterdam, 1998–1999, p. 9).

But the fundamental problem is of course more difficult because the longitudinal axis of the animal body and thus central nervous system typically is not straight. The longitudinal axis of all vertebrate embryos undergoes a complex change in shape during development (Figs. A.1d and A.3), and even the longitudinal axis of the adult rat is not straight (Figs. **A.2** lower left and A.3 lower right). However, there is a critical feature of the human body, and in particular of the human brain, that is responsible for serious confusion. There is an approximately 90-degree bend in the longitudinal axis of the human brain that occurs in the midbrain region (Fig. **A.2** lower right).

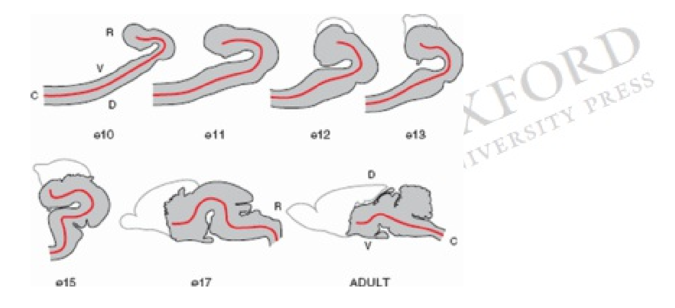




Figure A.3
During the course of embryogenesis the longitudinal axis (thick red line) of the neural tube undergoes major changes in shape. Key: C, caudal; D, dorsal; e10–e17, embryonic days 10–17; R, rostral; V, ventral. Adapted with permission from G. Alvarez-Bolado and L.W. Swanson, *Developmental Brain Maps: Structure of the Embryonic Rat Brain* (Elsevier: Amsterdam, 1996, p. 29).

Basically, the longitudinal axis of the spinal cord, medulla, and pons considered together is geographically vertical in the standing human, whereas the longitudinal axis of the forebrain is geographically horizontal. This is “because” the standing human is looking forward; the face is parallel to the belly instead of perpendicular as in the rat (Fig. **A.2**, lateral view at top). The practical consequence of this arrangement is that if a series of planes is drawn, or a series of histological sections is cut, through the human brain, they will start off “in front” (within the frontal pole of the forebrain) in a plane transverse to the longitudinal axis of the central nervous system, but then “in back” (in the pons, medulla, and spinal cord, and in the “back” half of the cerebrum and in the whole cerebellum) they will be parallel to the longitudinal axis. In comparative anatomical terms they will be transverse sections rostrally, frontal sections caudally, and a series of intermediate planes in between (where the superior and inferior colliculi lie).

Based on strict physical relationships it seems obvious that there can be no logically consistent way to apply a strict Cartesian coordinate system (with three standard, perpendicular planes) to the general vertebrate brain, or even to any individual species, if rostrocaudal actually refers to the longitudinal axis. Logically, the general solution would seem to lie in the topological relationships of parts, rather than in their geometrical (physical) relationships, which become distorted in unique ways in different groups of animals during embryogenesis. Such an approach is not yet common, although it has been adopted in this book.

Really effective description avoids slang. This is why the use in structural neuroscience of everyday terms like “in front of,” “behind,” “on top of,” or “under” should be strictly avoided. There is already enough confusion about the meaning of the technical terms discussed earlier. It is amazing how often the meaning of these common terms is very unclear, and thus textual descriptions are ambiguous, when reading the older neuroanatomical literature, and the same will eventually happen when they are used now.

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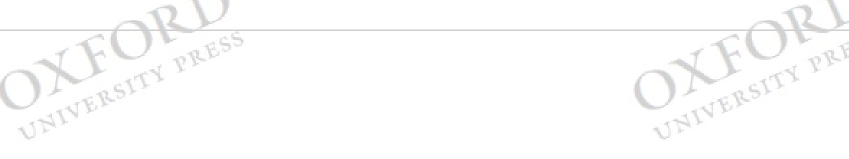






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Brain Architecture (2 ed.): Understanding the Basic Plan

Larry W. Swanson

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Naming and Classifying Nervous System Parts

> *"Among the various parts of the animated Body, which are subject to Anatomical disposition, none is presumed to be easier or better known than the Brain, yet in the meantime, there is none less or more imperfectly understood."*
>
> Thomas Willis (1681)
>
> *"The principal reason for the frequent disputes over terminology is not so much about whether a new term muddles Greek with Latin. It is really about whether the term is biased toward their theory rather than ours."*
>
> Marcus Jacobson (1993)

In Appendix A we dealt with the widespread confusion about how to describe position or location within the central nervous system. We go on now to discuss the more substantive yet even greater problems of inconsistent neuroanatomical nomenclature, and the lack of rigorous classification schemes for the various parts of the nervous system.

There is universal consternation when reading the highly international neuroanatomical literature about the meaning of terms that describe parts of the central nervous system. This is a problem that goes right back to the beginnings of the science in ancient Greece, but its magnitude can be glimpsed from the fact that over a century ago some 9000 terms had already been used to describe about 500 parts of the brain. According to Burt Wilder's Presidential Address to the American Neurological Association in 1885, there were in round numbers 2600 terms in Latin, 1300 in English, 2400 in German, 1800 in French, and 900 in Italian and Spanish. It is sobering to think how many terms may have been added since then. The number is entirely unknown but must be enormous—maybe over a million.

Unfortunately the problem is not with synonyms. There are indeed many synonyms, but they are relatively easy to deal with. The real problems come when the same term is used for different structures, when there are varying interpretations about the borders of particular structures and how those structures might be subdivided, when there are partial correspondences, and when authors use terms without defining them.

These have always been serious problems because they cause ambiguity in the data presented in the literature. As a result, readers can misinterpret data, or they may simply ignore a body of important data because it is difficult to interpret. However, they are even more serious now that massive electronic neuroscience databases are coming online.

When all is said and done the reason for this crippling situation is simple. It is not because anatomists are lazier, sloppier, or less critical than other scientists. After all, there is essentially no controversy about how to name the bones, muscles, and blood vessels. This has been settled for hundreds of years. The confusion in neuroanatomical nomenclature is due primarily to the fact that, unlike the skeletomotor and circulatory systems, we do not understand the basic organization of the nervous system. Stated another way, there are many, many areas of genuine controversy about the neuroanatomy of brain parts that await more data for resolution. After all, we are attempting to analyze an organ that is orders of magnitude more complex than any other part of the body, and from a realistic point of view we are only at the very initial stages of this analysis.

History has shown over and over again that attempts to enforce a rigid nomenclature on brain regional anatomy are doomed to failure, and for good reason. Our understanding of brain architecture is evolving quickly, and it is entirely possible that a majority of the nomenclature popular at the moment will not be relevant a century from now. Neuroanatomy has a specialized technical language of its own, and like any language it evolves. Particular terms are preferred when they are found useful by most people in the field. Because of the power of words in reifying concepts, it is a major mistake at this point in time to consider trying to enforce a "standard" nomenclature for the parts of the central nervous system. This can only impede progress in trying to understand the actual structure of the brain, as free as possible of preconceived biases.

This is not to say that all neuroanatomical terms are equally valid or that there is not a great deal that can be done to clarify neuroanatomical nomenclature. The single most important thing neuroscientists can do in this realm is to define the anatomical terms they use and to explain why they use the ones they do to the exclusion of others. And if new terms are introduced, they should be carefully defined with respect to existing terms, and reasons for introducing the new term should be given. Most readers will probably be appalled at the trivial nature of this suggestion. However, it is even more appalling how infrequently neuroanatomical terms are defined and, conversely, how often their meaning is unclear. To reiterate: this ambiguity is not due to the use of synonyms; it arises from differing interpretations of brain structure. The same word often has different or only partly corresponding meanings (structural interpretation) to different authors. The practical problem is this. When a neuroanatomical term is used in a specific paper, what does it mean to the author? There are almost always differing, critically unresolved views in the literature. This is the current state of neuroanatomy.

Many psychologists have argued that there is a natural tendency for the human mind to classify—it can't be helped. Thus, it comes as no surprise that there is a long history of attempts to classify the parts of the brain, although this went out of fashion in the latter half of the twentieth century. It stands to reason that classification schemes can only be as good as the data they are based on, and this may explain why there has been little interest in the topic lately. There is so much ambiguity in the literature, so many different

interpretations, that synthetic approaches have disappeared at the expense of reductionistic focusing on narrower and narrower problems. However, the reductionistic approach has produced in the last 25 years vast amounts of neuroanatomical data that are much more reliable than ever before, so the time may be ripe to revisit this problem.

Classification or taxonomy is an important, synthetic method of analysis. Look how influential Linnaeus's binomial nomenclature scheme was for biology or how seminal Mendeleev's periodic table of the elements was for chemistry. However, one must always bear in mind that any classification scheme inevitably reflects the biases of the author, just as the scheme inevitably imparts biases to those who study it. As a result, it is wise to subject any and all classification schemes to intense, ongoing scrutiny and comparison at the level of basic organizing principles.

This is especially true of schemes to classify the parts of the nervous system. There are a number of essentially different ways of grouping nervous system parts based, for example, on adult human regional anatomy, embryology and neuromeres, comparative and evolutionary neuroanatomy, and gene expression patterns (the genomic approach)—not to mention differing views within each of these broad categories. We have outlined one classification scheme in the book (see Figs. 5.10, 6.7, and B.1) and have presented detailed accounts elsewhere (see Swanson, 2003, and Swanson and Bota, 2010, in the list of readings at the end of this Appendix). However, it must be admitted that there is no irrefutable evidence for this, or any other, taxonomy of nervous system parts. It is presented as a model to stimulate further experimental work, and the formulation of alternative schemes. And the same limitation applies to the taxonomy of functional neural systems presented in Chapters 7–11. At the moment it seems to be the only modern global classification or model of nervous system network organization available. It begs replacement with a better one.







Figure B.1
Scheme for a basic taxonomy of nervous system parts in all animals, from hydra to human. The vertebrate central nervous system (cerebrospinal axis) is highlighted in blue. Adapted with permission from L.W. Swanson and M. Bota, Foundational model of nervous system structural connectivity: a schema for wiring diagrams, connectome, and basic plan architecture. *Proc. Natl. Acad. Sci. USA*, 2010 **107**:20610–20617.

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Methods for Analyzing Brain Architecture

"To examine each part [of the brain] thoroughly requires so much time and such application of mind that it would be necessary to give up all other labors and all other considerations on that particular task."

Nicolaus Steno (1669)

"As long as our brain is a mystery, the universe, the reflection of the structure of the brain, will also be a mystery."

Santiago Ramón y Cajal

"In the nervous system, we physiologists are more dependent upon what the anatomists tell us than we are anywhere else."

Sir John Eccles (1958)

Methods for analyzing nervous system structure divide broadly into two great classes. The oldest deals with topographic (regional) anatomy—what one can see with the naked eye by dissecting with knife, scraper, and probe. This approach is actually blossoming today thanks to exciting new technologies for functional brain imaging, where dissection is carried out algorithmically with computer graphics. However, around the middle of the nineteenth century it was supplemented and for many years largely overshadowed by revolutionary histological methods that allowed examination of neural tissue under the microscope, with orders of magnitude greater resolution. Thus began the era of cellular neuroscience that on the structural side has two branches, normal and experimental. Normal neurohistology deals with the microscopic appearance of neural tissue that has not been subjected to experimental manipulation like the production of lesions or the injection of pathway tracer injections. All scientific techniques have advantages and disadvantages, and it is critical to understand what they are and how to manage them. No problem can be solved unequivocally with a single technique. The strongest argument for any position always comes from independent verification with independent methods.

For understanding the three-dimensional architecture of the brain as an organ, nothing remotely compares to personal dissection. The human brain and the brains of animals like sheep and cows are large objects, and a truly remarkable amount of structural organization can be observed by careful dissection (easily on the order of 500 major parts). It is probably not possible to obtain a reasonable appreciation for the structure of the brain as an organ strictly from the examination of histological sections (even a complete series), or from artistic renderings. All of the major gray matter regions, and all of the major white matter tracts, can be examined with dissection, along with their fundamental shapes and topographic relationships. This is regional anatomy or architecture, and it is analogous to studying the distribution of land and water masses on a globe. It provides essential orientation for more detailed examination and description. The major limitation of this approach, obviously, is that it does not provide cellular resolution. It is not possible to determine the organization of neural networks with gross dissection (and by extension functional imaging methods alone, which actually have less resolution in common practice than naked eye examination of the brain).

Although the microscope was invented in the seventeenth century, virtually everything observed in the nervous system was artifactual until the 1820s when lenses that corrected serious spherical and chromatic aberrations began to be perfected in Germany. By the 1840s individual nerve fibers and neuron cell bodies had been observed under the microscope, in a variety of invertebrates and vertebrates, and it was then that Benedict Stilling (1810–1879) began his unparalleled examination of the human brainstem, cerebellum, and spinal cord. In this work, which was carried out over a period of more than 20 years, he examined under the microscope serial sections of this material cut in all three planes of section and described his results in a monumental series of books. Although no histological stains for neural tissue had yet been developed, he was able to see many neuron groups for the first time. For example, he discovered most of the cranial nerve nuclei, as well as other major cellular features of the brainstem, cerebellum, and spinal cord.

In 1858 Joseph von Gerlach (1820–1896) introduced the first stain of any value for neurohistological material, carmine. It had a selective affinity for certain tissue features, especially the cell nucleus, so that cell bodies were easier to observe in brain tissue sections. Considerably better stains for neuron cell bodies were not perfected until 1894 when Franz Nissl (1860–1919) published a full account of his basic aniline dye method, which we now know stains nucleic acids, both in the cell nucleus and in the ribosomes of the cytoplasmic endoplasmic reticulum. This simple, reproducible method remains a standard today. On the other side of the coin, Carl Weigert (1845–1904) introduced in 1882 a stain for myelinated fiber tracts that is still in use today, and about a decade later Cajal and Max Bielschowsky (1869–1940) introduced reduced silver methods for staining axons themselves. Variations on the Weigert, Cajal, Bielschowsky, and Nissl methods provided a wealth of information about the general distribution of neuron cell bodies and fiber tracts in the brain. However, they did not reveal the full morphology of individual neurons, or the organization of neural networks.

Three other normal histological approaches were indispensable. One was introduced by Golgi in 1873: the famous and revolutionary silver dichromate "black reaction," which for reasons still mysterious impregnates randomly about 1% of the neurons in a tissue block and impregnates them completely—axon (unmyelinated), cell body, and all dendrites. Golgi gave the first adequate description of axon collaterals with this method, and Cajal went on to show how neurons contact one another in all regions of the adult nervous system. His work remains the cornerstone of our understanding of the cellular architecture of neural networks. In 1886 Paul Ehrlich (1854–1915) introduced a

completely independent way to stain individual neurons completely, with methylene blue, and today they can be filled with markers using micropipettes that also record electrophysiological activity (and potentially obtain samples of intracellular content for molecular analysis). Together, these methods have been invaluable for determining the architecture of intraregional (local) circuitry. Until the last decade or so they have been much less useful in characterizing the long projections between gray matter regions.

The second major type of normal method is referred to as histochemical. Here chemical reactions are carried out on tissue sections and the sites of these reactions are labeled in one way or another so that they can be observed under the microscope. For example, with this approach it is possible to determine the distribution neuron by neuron of neurotransmitters and their receptors. The first systematic application of histochemistry to neuroanatomy was in the late 1950s and early 1960s by Shute and Lewis, who analyzed the central cholinergic system with a cholinesterase method in normal and experimentally lesioned animals. Today the most powerful histochemical techniques use antibodies to localize virtually any antigen of interest (immunohistochemistry), or they use complimentary strands of nucleic acids to localize specific mRNAs (in situ hybridization or hybridization histochemistry).

The final type of normal method was introduced in the 1950s: electron microscopy. It provided about three orders of magnitude greater resolution (from about 1 μm with light microscopy), so that for the first time the structure of synapses could be observed, along with that of the myelin sheath and many of the intracellular organelles.

Now we come to the so-called experimental neuroanatomical methods for analyzing the structure of neural networks. The incredibly complex meshwork of connections associated with neural networks has proven impossible to analyze reliably without experimental pathway tracing methods—false-positive results were greater than 80%. Experimental methods began with the demonstration by Augustus Volney Waller (1816–1870) in 1850–1851 that when a nerve is cut, the distal segment invariably degenerates. Ludwig Türck (1810–1868) independently and simultaneously used this approach in a brilliant way by making lesions in the spinal cord and observing the distribution of "Wallerian secondary degeneration" in the caudally directed tracts from the brain. In the 1880s Weigert attempted to trace pathways in the brain itself by making lesions and then observing the disappearance of fiber tracts with his myelin stain. Although a few things were discovered, it proved exceptionally difficult if not impossible to trace the loss of small tracts through the immense thicket of myelinated fibers distributed throughout the brain and spinal cord.

This problem was solved by Vittorio Marchi and Giovanni Algeri who introduced in 1885 a method for staining selectively just degenerating myelin, against a clear background of intact myelin. This approach has the obvious limitations that it does not reveal unmyelinated tracts, or the unmyelinated terminal regions of axons. This was not solved until the 1950s when Walle Nauta and Lloyd Ryan introduced the first selective stain for degenerating axons themselves.

What came to be called simply the Marchi and Nauta methods are based on the phenomenon of anterograde (Wallerian) axonal degeneration. Obviously, this approach relies on the interruption of fibers-of-passage (or the neuron cell bodies), and this is its greatest limitation. Very often the origins of fibers-of-passage were not known, and it was also common for fibers-of-passage of unknown origin to pass through the region of lesioned cell bodies. Thus, data from lesion experiments were either uninterpretable, or false-positive results were obtained.

These problems were beautifully solved beginning in the early 1970s by taking advantage of normal physiological processes in neurons, most notably fast intra-axonal transport mechanisms. The first really successful method was based on the uptake of radiolabeled amino acids microinjected into a neuron population whose projections were to be analyzed. The amino acids are taken up, incorporated into proteins, and shipped down the axon trunk and all its collaterals to the terminals, where they accumulate. The precise injection site and output pattern of the labeled neurons can then be reconstructed from autoradiograms of a series of sections cut through the brain. This method had two great advantages: it proved to be much more sensitive than the older lesion methods (it showed many more projections or network elements), and it did not involve fibers-of-passage because axons do not contain significant protein synthetic machinery. This critical feature eliminated the false-positive results so common with lesion methods.

The major disadvantage of the autoradiographic method was that the morphology of labeled outputs (axons and terminals) was not observed directly. Instead it had to be inferred from a pattern of silver grains. This problem has since been overcome with the introduction of other purely anterogradely transported tracers, most notably PHAL. This protein (which is a lectin) pathway tracer is detected with an antibody (immunohistochemically), and labeled axons from the very clearly defined injection site (group of neurons generating the labeled pathway pattern) are labeled with the clarity of a Golgi impregnation. Thus, the PHAL method amounts to an experimental Golgi method for long projections between neuron groups.

A second general strategy in experimental projection analysis was initiated by Bernhard von Gudden (1824–1886) in 1879. He observed that when certain cranial nerves are avulsed near their origin in newborn animals, retrograde degeneration may be observed in the brainstem motor neurons that give rise to the nerve. This demonstrated that in principle at least the origin of connections could be demonstrated by retrograde neuron degeneration, just as the course and termination of connections could be examined by anterograde axonal degeneration. In practice, however, very few connections in the central nervous system of adult animals undergo obvious retrograde degeneration. If an axon is cut after it generates a minimum number of collaterals, there is typically little obvious retrograde, cell body degeneration—which is referred to as chromatolysis.

A good solution to this problem also awaited the early 1970s, and this time used fast retrograde intra-axonal transport of injected markers. There are many such markers, including the protein horseradish peroxidase (HRP), and a wide variety of fluorescent dyes. They can be taken up by axon terminals and transported back to the cell bodies of origin, which can be observed by a variety of methods in histological sections under the microscope. This is an exceptionally powerful technique, although virtually all known tracers may be taken up to a greater or lesser extent by fibers-of-passage. This confounds the interpretation of results, but the best solution is to inject anterograde tracers into retrogradely labeled cell groups to confirm or discount the findings with an independent method. All pathways should eventually be subjected to both anterograde and retrograde tracer analysis because each method reveals different features of the pathway, and the methods confirm one another.

Today, anterograde and retrograde tracer analysis of neural networks—which can be extended to multiple coinjections (COINs) of anterograde and retrograde tracers in the same animal—is combined in the same tissue sections with histochemical methods to determine neurotransmitter content and other molecular features of particular connections. These combined methods can also, with a great deal of patience, be applied at the electron microscopic (ultrastructural) level to establish the structural arrangement of synaptic interactions. Furthermore, a whole new generation of intra-axonal transport methods for analyzing neural networks based on genetic engineering is coming online. The basic idea here is to take advantage of unique gene expression patterns in particular neuron types to generate endogenous tracer molecules restricted to that type. And finally, the birth of neuroinformatics, combined with high-throughput, high-resolution digital photography is spawning brain mapping projects on an unprecedented scale, from comprehensive gene expression pattern datasets to plans for complete tables of brain connections in worms, flies, mice, and people.

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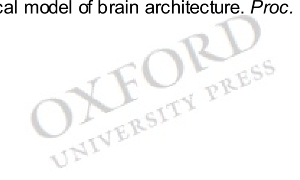
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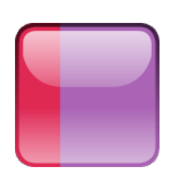
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Bandolier's Little Book of Making Sense of the Medical Evidence

Andrew Moore and Henry McQuay

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Glossary

Chapter: Glossary
Author(s): Andrew Moore and Henry McQuay
DOI: 10.1093/med/9780198566045.003.0008

We use an awful lot of jargon in science and medicine. It is inevitable to keep sentences and paragraphs short, but using a plethora of technical terms can lock newcomers out of the magic circle of initiated cognoscenti. The trouble is that resort to jargon can lead to other difficulties, mainly because people use the same jargon terms to describe different things; the result is confusion, a bit like the order, counterorder, disorder of the battlefield. As far as possible, key technical terms have been explained in the text. Some either have not been used, or perhaps we overlooked defining them. In any event, this glossary is intended as a place of sanctuary if all else fails.

Absolute risk reduction/increase. The absolute arithmetic difference in rates of bad outcomes between experimental and control participants in a trial, calculated as the experimental event rate (EER) and the control event rate (CER), and accompanied by a 95% CI. Depending on circumstances it can be reduction in risk (death or cardiovascular outcomes, for instance, in trials of statins) or an increase in benefit (pain relief, for instance, in trials of analgesics).

Adverse drug reaction. An appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product, that predicts hazard from future administration and warrants prevention or specific treatment or alteration of the dosage regimen or withdrawal of the product.

Adverse effect. As for adverse drug reaction, but applied to all interventions, not just drug interventions.

- The 'safety' of an intervention relates to its potential to cause serious adverse effects. 'Tolerability' relates to medically less important but unpleasant adverse effects of drugs. These include symptoms such as dry mouth, tiredness, etc. that can affect a person's quality of life and willingness to continue the treatment.
- A 'serious' adverse effect is one that has significant medical consequences, such as death, permanent disability, prolonged hospitalization. Indirect adverse effects, such as traffic accidents, violence, and damaging consequences of mood change, can also be serious.
- 'Severe' refers to the intensity of a particular adverse effect. For example, a non-serious adverse effect, such as headache, may be severe in intensity (as opposed to mild or moderate). A 'non-serious' effect, such as impotence, can have major consequences for a person's quality of life.

Adverse event. An adverse outcome occurring during or after the use of a drug or other intervention but not necessarily caused by it.

Average. A measure for the central tendency of a sample of observations. The term average is most often used for the arithmetic mean, but sometimes also for the median. For instance, suppose the yearly incomes of five people are $50,000, $80,000, $100,000, $120,000, and $650,000, respectively. The arithmetic mean is the sum of these values divided by the number of values, that is, $200,000. The median is obtained by ranking the values (as above) and taking the one in the middle, that is, $100,000. When the distribution is asymmetric, as it often is with income, the mean and the median are not the same, and it can be the case that most people earn less than the mean, with a few people having very high incomes.

Another example is with legs. Most people (99.9%) have two legs. But some have had amputations or accidents, so the average number of legs in the population is less than two. Therefore 99.9% of the population have more legs than average.

A priori. *A priori* comparisons are planned in advance of any data analysis. They are more reliable than *post hoc* comparisons.

Bayes theorem. Thomas Bayes (1702–61) was a mathematician who first used probability inductively and established a mathematical basis for probability inference (a means of calculating, from the number of times an event has not occured, the probability that it will occur in future trials). He set down his findings on probability in 'Essay towards solving a problem in the doctrine of chances' (1763), published posthumously in the *Philosophical Transactions of the Royal Society of London*. There is a whole school of Bayesian statistics, the subject of many books, though how much is due to Bayes and how much to Richard Price is another matter.

Richard Price was born in Tynton, Llangeinor, in 1723 and was friendly with Bayes before his death, and Bayes's relatives asked Price to examine his unpublished papers. Price realized their importance and submitted 'An essay towards solving a problem in the doctrine of chances' to the Royal Society. In this work Price, using the information provided by Bayes, introduced the idea of estimating the probability of an event from the frequency of its previous occurrences.

In 1765 Price was admitted to the Royal Society for his work on probability. He also began collecting information on life expectation and in May 1770 he wrote to the Royal Society about the proper method of calculating the values of contingent reversions. It is believed that this information drew attention to the inadequate calculations on which many insurance and benefit societies had recently been formed, and Price could be regarded as the father (or at least the midwife) of epidemiology. There have been suggestions that Price contributed more to what we know as Bayes theorem than Bayes himself did.

Bias. A dictionary definition of bias is 'a one-sided inclination of the mind'. It defines a systematic disposition of certain trial designs to produce results consistently better or

worse than other trial designs. Bias occurs in many different ways in all types of study, and avoiding or checking for known sources of bias is one of the most important elements in assessing the quality and validity of evidence. Unless it is done, it renders any evidence worthless.

Blinding. The process used in epidemiological studies and clinical trials in which the participants, investigators, and/or assessors remain ignorant concerning the treatments which participants are receiving. In single-blind studies only participants are blind to their allocations, while in double-blind studies at minimum the participants and assessors are blind to their allocations. Occasionally, even higher levels of blinding are found, when exigencies of design demand it.

Care pathway (or integrated care pathway). An integrated care pathway (ICP) is a multidisciplinary outline of anticipated care, placed in an appropriate timeframe, to help a patient with a specific condition or set of symptoms move progressively through a clinical experience to positive outcomes. Variations from the pathway may occur as clinical freedom is exercised to meet the needs of the individual patient.

ICPs are important because they help to reduce unnecessary variations in patient care and outcomes. They support the development of care partnerships and can empower patients and their carers. ICPs can also be used as a tool to incorporate local and national guidelines into everyday practice, manage clinical risk, and meet the requirements of clinical governance. When designing and introducing ICPs, it is important to incorporate them into organizational strategy and choose appropriate topics that will provide opportunities for improvement.

Case-control study. A study that involves identifying patients who have the outcome of interest (cases) and control patients who do not have that same outcome and looking back to see if they had the exposure of interest. The exposure could be some environmental factor, a behavioural factor, or exposure to a drug or other therapeutic intervention.

Case report. A report on a single patient with an outcome of interest.

Case series. A report on a series of patients with an outcome of interest. No control group is involved. For both case reports and case series there are useful guidelines about maximizing their evidential value.

Class effect. When it is assumed that all interventions of the same sort or with the same mechanism of action generate rather similar effects, or that particular effects both in nature and extent are associated with interventions of that type. Criteria for drugs to be grouped together as a class involve some or all of the following:

- drugs with similar chemical structure;
- drugs with similar mechanism of action;
- drugs with similar pharmacological effects.

Guidelines have been set out for what constitutes a class effect.

Clinical practice guideline. A systematically developed statement designed to assist clinician and patient decisions about appropriate health-care for specific clinical circumstances. Guidelines should be based on evidence, combined with local knowledge to ensure that they are appropriate for local conditions.

Clinical trial. A research study conducted with patients that tests out a drug or other intervention to assess its effectiveness and safety. Each trial is designed to answer scientific questions and to find better ways to treat individuals with a specific disease. This general term encompasses controlled clinical trials and randomized controlled trials.

A controlled clinical trial (CCT) is a study testing a specific drug or other treatment involving two (or more) groups of patients with the same disease. One (the experimental group) receives the treatment that is being tested, and the other (the comparison or control group) receives an alternative treatment, a placebo (dummy treatment), or no treatment. The two groups are followed up to compare differences in outcomes to see how effective the experimental treatment was. A CCT where patients are randomly allocated to treatment and comparison groups is called a randomized controlled trial.

Clouded thinking. A form of innumeracy, in which a person knows about the risks but not how to draw conclusions or inferences from them. For instance, physicians often know the error rates of mammography and the base rate of breast cancer, but not how to infer from this information the chances that a woman with a positive test actually has breast cancer. Mind tools for overcoming clouded thinking, such as natural frequencies, are representations that facilitate drawing conclusions.

Cohort study. Involves identification of two groups (cohorts) of patients —one that received the exposure of interest and one that did not—and following these cohorts forward for the outcome of interest.

Concealment of allocation. The process used to prevent foreknowledge of group assignment in a randomized controlled trial, which should be seen as distinct from blinding. The allocation process should be impervious to any influence by the individual making the allocation by having the randomization process administered by someone who is not responsible for recruiting participants, for example, a hospital pharmacy or a central office. Methods of assignment such as date of birth and case record numbers (see quasi-random allocation) are open to manipulation. Adequate methods of allocation concealment include: centralized randomization schemes; randomization schemes controlled by a pharmacy; numbered or coded containers in which capsules from identical-looking, numbered bottles are administered sequentially; on-site computer systems, where allocations are in a locked unreadable file; and sequentially numbered opaque, sealed envelopes.

Confidence interval (CI). Quantifies the uncertainty in measurement. It is usually reported as 95% CI, which is the range of values within which we can be 95% sure that the true value for the whole population lies. For example, for an NNT of 10 with a 95% CI of 5–15, we would have 95% confidence that the true NNT value was between 5 and 15.

A caveat is that the confidence interval relates to the population sampled. If we have a small sample of part of a population, or a very small sample of the whole population, then the confidence interval that is generated is not necessarily that for the whole population.

Conflict of interest. A conflict of interest occurs when those who are involved with the conduct or reporting of research also have financial or other interests, or where they can benefit in some other way, depending on the results of the research. The obvious example is where a company reports results of a trial of its product.

Conflict of interest statements often accompany published papers. They consist of a statement by a contributor to a report or review of personal, financial, or other interests that could have influenced the findings or their interpretation. Conflicts of interest are the norm, and not the exception.

The point about a conflict of interest is that a reader needs to know that it is there. It should not, and probably most of the time does not, impart any effect on the results of a trial. But it might, and if we discovered a conflict of interest at some later time, when it had been hidden, we would be concerned.

In relationships with industry, which often funds clinical trials or reviews, there are some things to look for. Most important is freedom to publish, whatever the result, the result of a trial or a review. That is the key element that most folks forget. If it is a review of otherwise unpublished material, it is worth looking for a declaration that all available trials had been made available.

Confounding. Confounding refers to a situation in which a measure of the effect of an intervention or exposure is distorted because of the association of exposure with other factor(s) that influence the outcome under investigation. This can lead to erroneous conclusions being drawn, particularly in observational studies.

Confounding by indication. This bias can arise in observational studies when patients with the worst prognosis are allocated preferentially to a particular treatment. These patients are likely to be systematically different from those not treated, or treated with something else.

CONSORT. The CONSORT statement is an important research tool that takes an evidence-based approach to improve the quality of reports of randomized trials. The statement is available in six languages and has been endorsed by prominent medical journals such as *The Lancet, Annals of Internal Medicine*, and the *Journal of the American Medical Association*. Its critical value to researchers, health-care providers, peer reviewers, journal editors, and health policy-makers is the guarantee of integrity in the reported results of research.

CONSORT comprises a checklist and flow diagram to help improve the quality of reports of randomized controlled trials. It offers a standard way for researchers to report trials. The checklist includes items, based on evidence, that need to be addressed in the report; the flow diagram provides readers with a clear picture of the progress of all participants in the trial, from the time they are randomized until the end of their involvement. The intent is to make the experimental process more clear, flawed or not, so that users of the data can more appropriately evaluate its validity for their purposes.

Control. A control is something against which we make a comparison. If we put large amounts of manure on our roses (an experimental group), we might want to find out what happened to roses on which no manure was used (control group). There can be all sorts of types and names for controls, some appropriate, others not.

- In clinical trials comparing two or more interventions, a control is a person in the comparison group who receives a placebo, no intervention, usual care, or another form of care.
- In case-control studies a control is a person in the comparison group without the disease or outcome of interest.
- In statistics control means to adjust for or take into account extraneous influences or observations.
- Control can also mean programmes aimed at reducing or eliminating the disease when applied to communicable (infectious) diseases.

Control event rate (CER). The rate at which events occur in a control group. It may be represented by a percentage (say, 10%) or as a proportion (when it is 0.1).

Cost–benefit analysis. Assesses whether the cost of an intervention is worth the benefit by measuring both in the same units; monetary units are usually used.

Cost-effectiveness analysis. Measures the net cost of providing a service as well as the outcomes obtained. Outcomes are reported in a single unit of measurement.

Cost minimization analysis. If health effects are known to be equal, only costs are analysed and the least costly alternative is chosen.

Cost utility analysis. Converts effects into personal preferences (or utilities) and describes how much it costs for some additional quality gain (e.g. cost per additional quality-adjusted life-year, or QALY).

Cox model. A Cox model is a well-recognized statistical technique for exploring the relationship between the survival of a patient and several explanatory variables.

- Survival analysis is concerned with studying the time between entry to a study and a subsequent event (such as death). Censored survival times occur if the event of interest does not occur for a patient during the study period.
- A Cox model provides an estimate of the treatment effect on survival after adjustment for other explanatory variables. It allows us to estimate the hazard (or risk) of death, or other event of interest, for individuals, given their prognostic variables.
- Even if the treatment groups are similar with respect to the variables known to affect survival, using the Cox model with these prognostic variables may produce a more precise estimate of the treatment effect (for example, by narrowing the confidence interval).
- Interpreting a Cox model involves examining the coefficients for each explanatory variable. A positive regression coefficient for an explanatory variable means that the hazard is higher, and thus the prognosis worse, for higher values. Conversely, a negative regression coefficient implies a better prognosis for patients with higher values of that variable.

Critical appraisal. The process of assessing and interpreting evidence by systematically considering its validity, results, and relevance. This sounds great, and often is. Of course, one needs to look at different forms of evidence differently—controlled trials versus observational studies, for instance, or diagnostic studies, or health economic studies. A number of schema have been developed for doing this, and are useful. The trouble is that any one of them can be wrong for a given paper, because some things are hard to define, such as what constitutes a valid or relevant study.

For evidence to be strong, it has to fulfil the requirements of all three of the following criteria—quality, validity, and size.

- Quality. Trials that are randomized and double-blind, to avoid selection and observer bias, and where we know what happened to most of the subjects in the trial.
- Validity. Trials that mimic clinical practice, or could be used in clinical practice, and with outcomes that make sense. For instance, in chronic disorders we want long—not short—term trials. We are not interested in small but marginally statistically significant ($p < 0.05$, say, or a 1 in 20 chance of being wrong) outcomes, but rather outcomes that are large, useful, and statistically very significant ($p < 0.01$, a 1 in 100 chance of being wrong).
- Size. Trials (or collections of trials) that have large numbers of patients, to avoid being wrong because of the random play of chance. For instance, be sure that a number needed to treat (NNT) of 2.5 is really between 2 and 3, we need results from about 500 patients. If that NNT is above 5, we need data from thousands of patients.

Cross-over study design. The administration of two or more experimental therapies one after the other in a specified or random order to the same group of patients. There are some important issues with cross-over designs. Two in particular often crop up.

- First is the issue of order effects, in which the order in which treatments are administered may affect the outcome. An example might be a drug with many adverse events given first making patients taking a second, less harmful medicine more sensitive to any adverse effect.
- Second is the issue of carry-over between treatments. In practice carry-over can be dealt with by use of a wash-out period between treatments, or by making observations sufficiently later after the start of a treatment period that any carry-over effect is minimized.

Cross-sectional study. The observation of a defined population at a signal point in time or time interval. Exposure and outcome are determined simultaneously.

Cumulative meta-analysis. In cumulative meta-analysis, studies are added one at a time in a specified order (e.g. according to date of publication or quality) and the results are summarized as each new study is added. In a graph of a cumulative meta-analysis, each horizontal line represents the summary of the results as each study is added, rather than the results of a single study.

Decision analysis (or clinical decision analysis). The application of explicit, quantitative methods that quantify prognoses, treatment effects, and patient values in order to analyse a decision under conditions of uncertainty.

Duplication. Trials can be reported more than once, a process known as duplication. Duplication can be justified, for instance, where results from a study at 2 years are followed later by results at 4 years. Another example might be reporting different results from a single trials (clinical or economic, for instance). But multiple publication can also be covert, and lead to overestimation of the amount of information available.

Ecological survey. A survey based on aggregated data for some population as it exists at some point or points in time: to investigate the relationship of an exposure to a known or presumed risk factor for a specified outcome.

Effect size. This is the standardized effect observed. By standardizing the effect, the effect size becomes dimensionless (and that can be helpful when pooling data). The effect size then becomes:

- a generic term for the estimate of effect for a study;
- a dimensionless measure of effect that is typically used for continuous data when different scales (e.g. for measuring pain) are used to measure an outcome and is usually defined as the difference in means between the intervention and control groups divided by the standard deviation of the control or both groups.

The effect size can be just the difference between the mean values of the two groups, divided by the standard deviation, as below, but there are other ways to calculate effect size in other circumstances.

Effect size = (mean of experimental group – mean of control group)/standard deviation.

Generally, the larger the effect size, the greater is the impact of an intervention. Jacob Cohen has written the most on this topic. In his well-known book he suggested, a little ambiguously, that a correlation of 0.5 is large, 0.3 is moderate, and 0.1 is small (Cohen, J. (1988). *Statistical power analysis for the behavioral sciences*, 2nd edn. Lawrence Erlbaum, New Jersey). The usual interpretation of this statement is that anything greater than 0.5 is large, 0.5–0.3 is moderate, 0.3–0.1 is small, and anything smaller than 0.1 is trivial. There is a good site that describes all this and is worth a visit for those really interested (*http://davidmlane.com/hyperstat/effect_ size.html*).

Empirical. Empirical results are based on experience (or observation) rather than on reasoning alone.

Epidemiology. The study of the distribution and determinants of health-related states or events in specified populations.

Error. A test can result in one of two errors, a false-positive or a false-negative. These errors can result from various sources, including human error (for example, the laboratory assistant confuses two samples or labels, or enters the wrong result on the computer) and medical conditions (for example, a positive HIV test can result from rheumatological diseases and liver diseases that have nothing to do with HIV). Errors can be reduced but not completely eliminated, and they may even be indispensable to adaptation and survival, as the copying errors (mutations) in DNA illustrate.

Event rate. The proportion of patients in a group in whom the event is observed. Thus, if out of 100 patients the event is observed in 27, the event rate is 0.27 or 27%. Control event rate (CER) and experimental event rate (EER) are used to refer to this in control and experimental groups of patients, respectively.

The patient expected event rate (PEER) refers to the rate of events we would expect in a patient who received no treatment or conventional treatment.

Evidence-based health-care. Extends the application of the principles of evidence-based medicine to all professions associated with health-care, including purchasing and management.

Evidence-based medicine. The conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients. The practice of evidence-based medicine means integrating individual clinical expertise with the best available external clinical evidence from systematic research. Evidence-based medicine does not mean ‘cook-book’ medicine, or the unthinking use of guidelines. It does imply that evidence should be reasonably readily available in an easily understood and useable form.

Experimental event rate (EER). The rate at which events occur in an experimental group. It may be represented by a percentage (say, 50%) or as a proportion (when it is 0.5).

False-negative. A test result in which the test is negative (for example, a pregnancy test finds no sign of pregnancy) but the event is actually there (the woman is pregnant)—also called a ‘miss’. The proportion of negative tests among people with the disease of the condition. It is typically expressed as a conditional probability or a percentage. For instance, mammography screening has a false-negative rate of 5–20% depending on age, that is, 5–20% of women with breast cancer receive a negative test result. The false-negative rate and the sensitivity (hit rate) of a test add up to 100%. The false-negative rate and the false-positive rate are dependent: to decrease one is to increase the other.

False-positive. A test result in which the test is positive (for example, a positive pregnancy test) but the event is not extant (the woman is not pregnant)—also called a ‘false alarm’. The trouble with false-positives is that the more you test the more apparent disease you find, also called a *false-positive explosion*. The proportion of positive tests among people without the disease or condition. It is typically expressed as a conditional probability or a percentage. For instance, mammography screening has a false-negative rate of 5–10% depending on age, that is, 5–0% of women without breast cancer nevertheless receive a positive test result. The false-positive rate and the specificity (power) of a test add up to 100%. The false-positive rate and the false-negative rate are dependent: to decrease one is to increase the other.

Fixed effects model. This is a statistical model that stipulates that the units under analysis (people in a trial or study in a meta-analysis) are the ones of interest and thus constitute the entire population of units. Only within-study variation is taken to influence the uncertainty of results (as reflected in the confidence interval) of a meta-analysis using a fixed effect model. Variation between the estimates of effect from each study (heterogeneity) does not affect the confidence interval in a fixed effect model.

Framing. There has been research on the interpretation of numerical information and how that depends on the presentation of the information. Technically this is known as framing, and the effects of framing generally show that relative outputs, such as relative risk, odds ratios, or NNTs, are more likely to be influential than absolute outputs such as percentages or proportions of patients who benefit, or absolute risk reduction or increase.

Franklin's law. ‘Nothing is certain but death and taxes.’ A reminder that, in all human contact, uncertainty is prevalent as the result of human and technical errors, limited knowledge, unpredictability, deception, or other causes. Always useful to bear in mind when people talk glibly about reducing mortality: we may put it off, but the rate stubbornly stays close to 100% if you wait long enough.

Frequencies. A number of observations in a class of events. Frequencies can be expressed as relative frequencies, absolute frequencies, or natural frequencies.

Natural frequencies are numbers that correspond to the way humans encountered information before the invention of probability theory. Unlike probabilities and relative frequencies, they are raw observations that have not been normalized with respect to the base rates of the event in question.

Relative frequencies are one of the three major interpretations of probability (the others are degrees of belief and propensities). The probability of an event is defined as its relative frequency in a reference class. Historically, frequencies entered probability theory through mortality tables that provided the basis for calculating life insurance rates. Relative frequencies are constrained to repeated events that can be observed in large numbers.

Gold standard. A method, procedure, or measurement that is widely accepted as being the best available.

Heterogeneity. In systematic reviews heterogeneity refers to variability or differences between studies in the estimates of effects. A distinction should made between ‘statistical heterogeneity’ (differences in the reported effects), ‘methodological heterogeneity’ (differences in study design), and ‘clinical heterogeneity’ (differences between studies in key characteristics of the participants, interventions, or outcome measures). Where there are large differences in clinical or methodological nature between studies, the simplest question to ask is whether there is any good reason for pooling data from these studies in a meta-analysis where heterogeneity is known to exist.

More difficult is the occurrence of statistical heterogeneity where there is methodological and clinical homogeneity. Statistical tests of heterogeneity are used to assess whether

the observed variability in study results (effect sizes) is greater than that expected to occur by chance. These tests have low statistical power, and the boundary for statistical significance is usually set at 10%, or 0.1. Some people think that if these tests are used, then a value of 1%, or 0.01 makes more sense.

An analysis of the performance of commonly used tests shows that the Breslow–Day test performs most consistently (Gavaghan, D.J. *et al*. (2000). An evaluation of homogeneity tests in meta-analysis in pain using simulations of individual patient data. *Pain* **85**, 415–24).

Homogeneity. In systematic reviews homogeneity refers to the degree to which the results of studies included in a review are similar. Clinical homogeneity means that, in trials included in a review, the participants, interventions, and outcome measures are similar or comparable. Studies are considered statistically homogeneous if their results vary no more than might be expected by the play of chance, though most statistical tests would say that 10% of a perfectly homogeneous data set was heterogeneous, because that is the usual set-point for the tests.

Impact factor. An impact factor for a journal attempts to provide a measure of how frequently papers published in a journal are cited in the scientific literature. It is derived by dividing the number of citations in any 1 year with items published in the journal in the previous 2 years. The calculation is as follows:

A Total literature citations to substantive items published in a journal in 2003.

B Number of citations in A that refer to articles published in 2001 and 2002.

C Number of substantive articles published in the journal in 2001 and 2002.

The impact factor is then B divided by C, and gives the average number of times an article published in the journal in 2001 and 2002 has been cited in 2003. Thus, if there were 1000 citations in 2003 for 100 articles published in a journal in 2001 and 2002, the impact factor would be 10. Most journals (and there are many, many journals) have impact factors that are below 2. Journals with impact factors above 4 tend to be regarded as having a high impact factor, and those above 10 are stellar (see Garfield, E. (1994). The impact factor. *Current Contents* **20**, 3–7).

Inception cohort. A group of patients who are assembled near the onset of the target disorder.

Incidence. The proportion of new cases of a particular disease or condition in a population during a specified time interval. It is usual to define the disorder, and the population, and the time, and report the incidence as a rate.

Individual patient data. In systematic reviews this term refers to the availability of raw data for each study participant in each included trial, as opposed to aggregate data (summary data for the comparison groups in each study). Reviews using individual patient data require collaboration of the investigators who conducted the original trials, who must provide the necessary data.

Intention-to-treat analysis (ITT). A method of analysis for randomized trials in which all patients randomly assigned to one of the treatments are analysed together, regardless of whether or not they completed or received that treatment. This is a complex area, and there are many definitions of what constitutes ITT. Consider a typical migraine trial, in which patients are randomized in groups, given a tablet, and told to take it if they have a migraine. Some people have a migraine and take the tablet. Some do not have a migraine and do not take the tablet. Is the proper analysis on the number randomized or the number of those randomized who actually had a migraine? There is no simple answer as to what is correct.

Independence. Two events are independent if knowing the outcome of one does not inform us about the outcome of the other. Formally, two events A and B are independent if the probability *p*(A & B) that A and B occur together is the product of *p*(A) times *p*(B). The concept of independence is crucial, for instance, to evaluating a match between a defendant's DNA and that found on a victim.

Assume only 1 out of 1 million men show such a match. If the DNA of all of a country's citizens are in a data bank, and one citizen's DNA is randomly selected, then the probability of a match is about 1 in a million. If the defendant, however, has an identical twin, the probability that the twin also shows a match is 1 (except for procedural errors), not 1 in 1 million. Similarly, if the defendant has brothers, the probability that they match is considerably higher than for the general population. The DNA of relatives is not independent; knowing that one matches increases the chances that the relative also matches.

L'Abbé plot. A first stage in any review is to look at a simple scatter plot, which can yield a surprisingly comprehensive qualitative view of the data. Even if the review does not show the data in this way you can do it from information on individual trials presented in the review tables. A L'Abbé plot simply shows the scatter of trials according to outcomes for intervention and control. Visual inspection gives a quick and easy indication of the level of agreement among trials. Heterogeneity is often assumed to be due to variation in the experimental and control event rates, but that variation is often due to the small size of trials.

Likelihood ratio. The likelihood that a given test result would be expected in a patient with the target disorder compared with the likelihood that the same result would be expected in a patient without the target disorder.

Longitudinal study. A study of the same group of people at more than one point in time. (This type of study contrasts with a cross-sectional study, which observes a defined set of people at a single point in time.)

Mean. The average value, calculated by adding all the observations and dividing by the number of observations.

Median. Middle value of a list. If you have numbers 2, 3, 4, 5, 6, 7, and 8, the median is 5. Medians are often used when data are skewed, meaning that the distribution is uneven. In that case, a few very high numbers could, for instance, change the mean, but they would not change the median.

Other definitions include the smallest number such that at least half the numbers in the list are no greater than it. If the list has an odd number of entries, the median is the middle entry in the list after sorting the list into increasing order. If the list has an even number of entries, the median is equal to the sum of the two middle (after sorting) numbers divided by two. The median can be estimated from a histogram by finding the smallest number such that the area under the histogram to the left of that number is 50%. But all mean the same thing in the end.

Meta-analysis. A systematic review that uses quantitative methods to summarize the results. A meta-analysis is where we pool all the information we have from a number of different (but similar) studies. It should not be about adding small piles of rubbish together to make a big pile of rubbish. It is only worth doing when individual trials are themselves of sufficient quality and validity. What meta-analysis does is to give enough size to have the power to see the result clearly, without the noise of the random play of chance.

Any meta-analysis must have enough events to make sense. Combining small, poor, trials with few events will mislead.

Mode. For lists, the mode is the most common (frequent) value.

MOOSE. Guidelines for reporting meta-analysis of observational studies.

***N*-of-1 trials**. In such trials, the patient undergoes pairs of treatment periods organized so that one period involves the use of experimental treatment and the other involves the use of an alternate or placebo therapy. The patient and physician are blinded, if possible, and outcomes are monitored. Treatment periods are replicated until the clinician and patient are convinced that the treatments are definitely different or definitely not different.

Negative predictive value. Proportion of people with a negative test who are free of the target disorder.

Null hypothesis. In simplest terms, the null hypothesis states that the results observed in a study are no different from what might have occurred as a result of the play of chance. More formally, the statistical hypothesis that one variable (e.g. whether or not a study participant was allocated to receive an intervention) has no association with another variable or set of variables (e.g. whether or not a study participant died) or that two or more population distributions do not differ from one another.

Number needed to harm (NNH). This is calculated in the same way as for NNT (see next entry), but used to describe adverse events. For NNH, large numbers are good, because they mean that adverse events are rare. Small values for NNH are bad, because they mean adverse events are common.

Number needed to treat (NNT). The inverse of the absolute risk reduction or increase and the number of patients that need to be treated for one to benefit compared with a control. The ideal NNT is 1, where everyone has improved with treatment and no one has with control. The higher the NNT, the less effective is the treatment. But the value of an NNT is not just numeric. For instance, NNTs of 2–5 are indicative of effective therapies, such as analgesics for acute pain. NNTs of about 1 might be seen by treating sensitive bacterial infections with antibiotics, while an NNT of even 40 or more might be useful, as when using aspirin after a heart attack.

Observational study. In research about diseases or treatments, this refers to a study in which nature is allowed to take its course. Changes or differences in one characteristic (e.g. whether or not people received a specific treatment or intervention) are studied in relation to changes or differences in other(s) (e.g. whether or not they died) without the intervention of the investigator. There is a greater risk of selection bias than in experimental studies.

Odds. A ratio of the number of people incurring an event to the number of people who have no events.

Odds ratio. The ratio of the odds of having the target disorder in the experimental group relative to the odds in favour of having the target disorder in the control group (in cohort studies or systematic reviews) or the odds in favour of being exposed in subjects with the target disorder divided by the odds in favour of being exposed in control subjects (without the target disorder).

***p*-value**. The probability (ranging from zero to one) that the results observed in a study (or results more extreme) could have occurred by chance. Convention is that we accept a *p*-value of 0.05 or below as being statistically significant. That means a chance of 1 in 20, which is not very unlikely. This convention has no solid basis, other than being the number chosen many years ago. When many comparisons are being made, statistical significance can occur just by chance. A more stringent rule is to use a *p*-value of 0.01 (1 in 100) or below as statistically significant, though some folk get hot under the collar when you do it.

Peer review. Review of a study, service, or recommendations by those with similar interests and expertise to the people who produced the study findings or recommendations. Peer reviewers can include professional, patient, and carer representatives. The trouble is that peer review does not always (or even frequently) work very well. Many poor papers are published, and even papers published in top medical journals can have major flaws. Just because something is found in a peer-reviewed journal does not mean it is right, or good, or sensible.

Phases in drug development

- Phase I studies. The first stage in testing a new drug in humans. Usually performed on healthy volunteers without a comparison group.
- Phase II studies. Second stage in testing a new drug in humans. These are often randomized controlled trials, and often performed in patients with the condition of interest. Typically they will be studies of shorter duration or will examine dose–response relationships.
- Phase III studies. Studies that are a full-scale evaluation of treatment. After a drug has been shown to be reasonably effective, it is essential to compare it to the current standard treatments for the same condition. Phase III studies are usually randomized controlled trials, and are of longer duration, and larger than phase II studies.
- Phase IV studies. Studies that are concerned with post-marketing surveillance. They are often promotional exercises aimed at bringing a new drug to the attention of a large number of clinicians, and may be of limited scientific value. Phase IV studies may also be conducted in slightly different populations for licence extensions.

Placebo. A placebo is a fake or inactive intervention, received by the participants allocated to the control group in a clinical trial, that is indistinguishable from the active intervention received by patients in the experimental group. One definition is that use of a placebo describes what happens when you do nothing so that, in the context of a clinical trial, for instance, a placebo group could describe the natural history of a disorder without the intervention under test.

Point estimate. The results (e.g. mean, weighted difference, odds ratio, relative risk, or risk difference) obtained in a sample (a study or a meta-analysis), which are used as the best estimate of what is true for the relevant population from which the sample is taken. A confidence interval is a measure of the uncertainty (due to the play of chance) associated with that estimate.

Positive predictive value. Proportion of people with a positive test who have the target disorder.

Pre- and post-test odds

- Pre-test odds. The odds that the patient has the target disorder before the test is carried out (pre-test probability/[1 – pre-test probability]).
- Post-test odds. The odds that the patient has the target disorder after the test is carried out (pre-test odds × likelihood ratio).

Pre- and post-test probability

- Pre-test probability. The proportion of people with the target disorder in the population at risk at a specific time (point prevalence) or time interval (period prevalence). Prevalence may depend on how a disorder is diagnosed.
- Post-test probability. The proportion of patients with that particular test result who have the target disorder (post-test odds/[1 + post-test odds]).

Precision. Precision is a term that can have slightly different meanings, depending on the context in which it is used. Some would argue that what we should be talking about is imprecision—the propensity of any series of measurements to get different answers. If we measure the same thing in the same (or different) ways, we expect to get the same answer. Often we do not. Here are some definitions.

1. A measure of the closeness of a series of measurements of the same material. In laboratories precision is expressed as a coefficient of variation, which is nothing more than the standard deviation divided by the mean and expressed as a percentage.
2. A measure of the likelihood of random errors in the results of a study, meta-analysis, or measurement. Confidence intervals around the estimate of effect from each study are a measure of precision, and the weight given to the results of each study in a meta-analysis (typically the inverse of the variance of the estimate of effect) is a measure of precision (i.e. the degree to which a study influences the overall estimate of effect in a meta-analysis is determined by the precision of its estimate of effect). (Note: faked studies are often very precise, and can be given disproportionate weight in meta-analysis. Very great precision is not a feature of biological systems, and should be looked at with a cold and fishy eye.)
3. The proportion of relevant citations located using a specific search strategy (i.e. the number of relevant studies meeting the inclusion criteria for a trials register or a review) divided by the total number of citations retrieved.

Prevalence. This is a measure of the proportion of people in a population who have a particular disease at a point in time, or over some period of time.

Probability. A measure that quantifies the uncertainty associated with an event.

- If an event A cannot happen, the probability *p*(A) is zero.
- If an event happens with certainty, *p*(A) is 1.
- Otherwise the values of *p*(A) are between zero and 1.

For a set of events, A and B that are mutually exclusive and exhaustive, the probabilities of the individual events add up to 1. Probabilities can also be expressed as percentages, when the sum of all probabilities is 100%.

- Prior probability. The probability of an event before new evidence. Bayes's rule specifies how prior probabilities are updated in the light of new evidence.
- Posterior probability. The probability of an event after a diagnostic result, that is, the updated prior probability. It can be calculated from the prior probability using Bayes's rule.
- Conditional probability. The probability that an event A occurs given event B, usually written *p*(A|B). An example of a conditional probability is the probability of a positive screening mammogram given breast cancer, which is around 0.9. The probability *p*(A), for instance, is not a conditional probability. Conditional probabilities are notoriously misunderstood, and that in two different ways. One is to confuse the probability of A given B with the probability of A and B; the other is to confuse the probability of A given B with the probability of B given A. One can reduce this confusion by replacing conditional probabilities with **natural frequencies**.

Programme budgeting and marginal analysis. Programme budgeting and marginal analysis (PBMA) is a process that helps decision-makers maximize the impact of health-care resources on the health needs of a local population.

Programme budgeting is an appraisal of past resource allocation in specified programmes, with a view to tracking future resource allocation in those same programmes. Marginal analysis is the appraisal of the added benefits and added costs of a proposed investment (or the lost benefits and lower costs of a proposed disinvestment).

Prospective study. In evaluations of the effects of health-care interventions, a study in which people are divided into groups who are exposed or not exposed to the intervention(s) of interest before the outcomes have occurred. Randomized controlled trials are always prospective studies and case-control studies never are. Concurrent cohort studies are prospective studies, whereas historical cohort studies are not (see cohort study), although in epidemiology a prospective study is sometimes used as a synonym for cohort study.

Protocol. This is the plan or set of steps to be followed in a study. In a clinical trial the protocol should, as a minimum, set out the study design, the entry criteria for patients and any exclusion criteria, the treatments, dose, duration, outcomes (both efficacy and adverse events, and how they are to be measured), and analysis plan.

A protocol for a systematic review should describe the rationale for the review; the objectives; and the methods that will be used to locate, select, and critically appraise studies and to collect and analyse data from the included studies.

Protocols can, and probably should, be amended. A plan may change because the nature of a trial or review changes. The key thing is that the amendments to the protocol need to be noted, together with the reasons. Protocols are good things because they make you think about what you are going to do, and why.

QALY. Quality-adjusted life year.

Qualitative and quantitative research

- Qualitative research is used to explore and understand people's beliefs, experiences, attitudes, behaviour, and interactions. It generates non-numerical data, e.g. patients' descriptions of their pain rather than a measure of pain. In health-care, qualitative techniques have been commonly used in research documenting the experience of chronic illness and in studies about the functioning of organizations. Qualitative research techniques such as focus groups and in-depth interviews have been used in one-off projects commissioned by guideline development groups to find out more about the views and experiences of patients and carers.
- Quantitative research generates numerical data or data that can be converted into numbers, for example, clinical trials or the National Census, which counts people and households.

Quality of life. Quality of life is a descriptive term that refers to an individual's emotional, social, and physical well-being, and his/her ability to function in the ordinary tasks of living.

Quality scoring. If studies are not done properly, any results they produce will be worthless. We call this validity. What constitutes a valid study depends on many factors; there are no absolute hard and fast rules that can cover every clinical eventuality. Validity has a dictionary definition of 'sound and defensible'. But the quality of study conduct and reporting is also important, because incorrect conduct can introduce bias. Bias has a dictionary definition of a one-sided inclination of the mind, and studies with bias may be wrong even if the study is valid.

Random effect mode. This is a statistical model sometimes used in meta-analysis in which both within-study sampling error (variance) and between-studies variation are included in the assessment of the uncertainty (confidence interval) of the results of a meta-analysis. If there is significant heterogeneity among the results of the included studies, random-effect models will give wider confidence intervals than fixed effect models.

Randomization (or random allocation). Method analogous to tossing a coin to assign patients to treatment groups (the experimental treatment is assigned if the coin lands heads and a conventional, control, or placebo treatment is given if the coin lands tails). Usually done by using a computer that generates a list of random numbers that can then be used to generate a treatment allocation list.

- Randomized controlled clinical trial (RCT). A group of patients is randomized into an experimental group and a control group. These groups are followed up for the variables/outcomes of interest. The point about using randomization is that it avoids any possibility of selection bias in a trial. The test that randomization has been successful is that different treatment groups have the same characteristics at baseline. For instance, there should be the same number of men and women, or older or younger people, or different degrees of disease severity.
- Quasi-random allocation. A method of allocating participants to different forms of care that is not truly random—for example, allocation by date of birth, day of the week, medical record number, month of the year, or the order in which participants are included in the study (alternation). A quasi-randomized trial uses a quasi-random method of allocating participants to different interventions. There is a greater risk of selection bias in quasi-random trials where allocation is not adequately concealed compared with randomized controlled trials with adequate allocation concealment.
- Stratified randomization. In any randomized trial it is desirable that the comparison groups should be as similar as possible as regards those characteristics that might influence the response to the intervention. Stratified randomization is used to ensure that equal numbers of participants with a characteristic thought to affect prognosis or response to the intervention will be allocated to each comparison group. For example, in a trial of women with breast cancer, it may be important to have similar numbers of pre-menopausal and post-menopausal women in each comparison group. Stratified randomization could be used to allocate equal numbers of pre- and post-menopausal women to each treatment group. Stratified randomization is performed either by performing separate randomization (often using random permuted blocks) for each strata, or by using minimization.

Relative risk. The ratio of risk in the treated group (EER) to risk in the control group (CER). Relative risk = EER/CER. It is used in randomized trials and cohort studies.

Relative risk reduction. The relative risk reduction is the difference between the EER and CER (EER – CER) divided by the CER, and usually expressed as a percentage.

Retrospective study. A retrospective study deals with the present and past and does not involve studying future events. This contrasts with studies that are prospective.

Risk factor. An aspect of a person's condition, lifestyle, or environment that increases the probability of occurrence of a disease. For example, cigarette smoking is a risk factor for lung cancer.

Screening. The testing of a symptomless population in order to detect cases of a disease at an early stage. The basic principles of screening are:

- The condition is common and disabling, the natural history is known, and there is a recognizable latent or pre-symptomatic phase.
- The screening test is reliable, valid, and repeatable; is acceptable and easy to perform; and is sensitive, specific, and low-cost.
- The treatment should be effective and available, and there should be an agreed policy on whom to treat.

The term screening is also used outside of medicine, for instance, when a population is screened for a DNA profile.

Selection bias. In assessments of the validity of studies of health-care interventions, selection bias refers to systematic differences between comparison groups in prognosis or responsiveness to treatment. Random allocation with adequate concealment of allocation protects against selection bias. Other means of selecting who receives the intervention of interest, particularly leaving it up to the providers and recipients of care, are more prone to bias because decisions about care can be related to prognosis and responsiveness to treatment.

Selection bias is sometimes used to describe a systematic error in reviews due to how studies are selected for inclusion. Publication bias is an example of this type of selection bias.

Selection bias, confusingly, is also sometimes used to describe a systematic difference in characteristics between those who are selected for study and those who are not. This affects the generalizability (external validity) of a study but not its (internal) validity.

Selection criteria. Explicit standards used by reviewers to decide which studies should be included and excluded from consideration as potential sources of evidence.

Sensitivity. Proportion of people with the target disorder who have a positive test. It is used to assist in assessing and selecting a diagnostic test/sign/symptom.

Sensitivity analysis. An analysis used to determine how sensitive the results of a study or systematic review are to changes in how it was done, such as using only randomized trials compared with non-randomized, or double-blind compared with open, or large versus small studies. Sensitivity analyses are used to assess how robust the results are to uncertain decisions or assumptions about the data and the methods that were used. Criteria on which sensitivity analysis may be based include (but are not limited to):

- random versus non-random studies;
- blind versus open studies;
- dose of intervention;
- duration of intervention;
- duration of observations;
- severity of condition at start of a trial;
- magnitude of outcome;
- size of trial;
- geographical location of study;
- quality of study;
- validity of study.

SnNout. When a sign/test/symptom has a high *sensitivity*, a *negative* result rules out the diagnosis. For example, the sensitivity of a history of ankle swelling for diagnosing ascites is 93%; therefore, if a person does not have a history of ankle swelling, it is highly unlikely that the person has ascites.

Specificity. Proportion of people without the target disorder who have a negative test. It is used to assist in assessing and selecting a diagnostic test/sign/symptom.

Spectrum bias. An unrecognized (but probably very real) problem is that of spectrum bias. This is the phenomenon of the sensitivity and/or specificity of a test varying with different populations tested—populations who might vary in sex ratios, age, or severity of disease as three simple examples.

SpPin. When a sign/test/symptom has a high *specificity*, a *positive* result rules in the diagnosis. For example, the specificity of a fluid wave for diagnosing ascites is 92%; therefore, if a person does have a fluid wave, it rules in the diagnosis of ascites.

Statistical power. The ability of a study to demonstrate an association or causal relationship between two variables, given that an association exists. For example, 80% power in a clinical trial means that the study has a 80% chance of ending up with a *p*-value of less than 5% in a statistical test (i.e. a statistically significant treatment effect) if there really was an important difference (e.g. 10% versus 5% mortality) between treatments. If the statistical power of a study is low, the study results will be questionable (the study might have been too small to detect any differences). By convention, 80% is an acceptable level of power.

Surrogate endpoints. Outcome measures that are not of direct practical importance but are believed to reflect outcomes that are important are called surrogate outcomes. For instance, cholesterol is used as a surrogate endpoint in many trials where cholesterol reduction is used as a surrogate for reduced mortality. The trouble is that trials to demonstrate mortality reduction have to be large and long. Cholesterol reduction is known to be strongly associated with mortality benefits, and can be measured easily in smaller numbers of patients. In another example, blood pressure is not directly important to patients but it is often used as an outcome in clinical trials because it is a risk factor for stroke and heart attacks.

Surrogate endpoints are often physiological or biochemical markers that can be relatively quickly and easily measured, and that are taken as being predictive of important clinical outcomes. They are often used when observation of clinical outcomes requires long follow-up. The main thing to remember is that there has to be a good reason to accept a surrogate endpoint. We have to be sure that the utility of the surrogate is well established.

Systematic review. A summary of the medical literature that uses explicit methods to perform a thorough literature search and critical appraisal of individual studies and that uses appropriate statistical techniques to combine these valid studies.

Uncertainty. An event or outcome that is not certain but may or may not happen is uncertain. When the uncertainty is quantified on the basis of empirical observations, it is called risk.

Utility. In economic and decision analysis, the desirability of an outcome, usually expressed as being between zero and one (e.g. death typically has a utility value of zero and a full healthy life has a value of one).

Validity. This term is a difficult concept in clinical trials, but refers to a trial being able to measure what it sets out to measure. A trial that set out to measure the analgesic effect of a procedure might be in trouble if patients had no pain. Or in a condition where treatment is life-long, evaluating an intervention for 10 minutes might be seen as silly.

Variable. A measurement that can vary within a study, e.g. the age of participants. Variability is present when differences can be seen between different people or within the same person over time, with respect to any characteristic or feature that can be assessed or measured.

Variance. A measure of the variation shown by a set of observations, defined by the sum of the squares of deviations from the mean, divided by the number of degrees of freedom in the set of observations.

Weighted mean or weighted mean difference

In meta-analysis, information to be pooled can either be dichotomous (how many patients die, say, out of a total number) or continuous (the mean cholesterol was *X* mmol/L, with some estimate of variance).

For continuous variables we need to combine measures, where the mean, standard deviation and sample size in each group are known. The weight given to each study (how much influence each study has on the overall results of the meta-analysis) is determined by the precision of its estimate of effect and, in the statistical software in RevMan, is equal to the inverse of the variance. This method assumes that all of the trials have measured the outcome on the same scale.

The weighted mean could be calculated for groups before and after an intervention (such as blood pressure lowering), and the weighted mean difference would be the difference between start and finish values. For this, though, the difference would usually be calculated not as the difference between the overall start value and the overall final value, but rather as the sum of the differences in the individual studies, weighted by the individual variances for each study.

Precision is not the only way of calculating a weighted mean or weighted mean difference. Another, simpler, way is to weight by the number in the study. This is a defence against giving undue weight to small studies of low variance where there may have been less than robust treatment of data and where people could have cheated.







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